Lecture Note		
Subject: Ph.Cology, 404T	**SEM-4th**	**UNIT-II**
Submitted By:	**Prasenjit Mishra**	**HCP-345-BBSR**

Adverse drug Reaction

An adverse drug event is "Each noxious health event, which can occur during therapy, but doesn´t have to have relation with this therapy".

An adverse drug reaction is a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function." Note that there is a causal link between a drug and an adverse drug reaction.

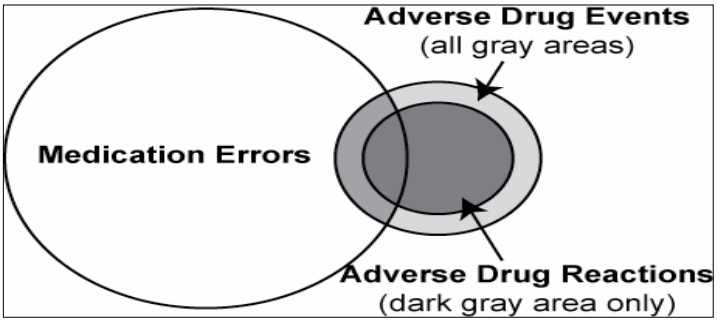
As per WHO: any response to a drug which is noxious and Unintended and which occurs at doses used in
man for prophylaxis, diagnosis or therapy.

As per Directive 2010/84/EU: adverse reaction – noxious and unintended effects resulting not only for the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.

An allergy is an adverse drug reaction mediated by an immune response (e.g., rash, hives).

A side effect is each unintend drug effect, occuring at normal doses used for patients, which is in relation to pharmacologic properties of drug.

Medication errors are mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Examples of medication errors include misreading or miswriting a prescription. Medication errors that are stopped before harm can occur are sometimes called "near misses" or "close calls" or more formally, a potential adverse drug event. Not all prescribing errors lead to adverse outcomes. Some do not cause harm, while others are caught before harm can occur ("near-misses").



Onset of reaction

Acute	within 60 minutes
Sub-acute	1 to 24 hours
Latent	> 2 days

Classification of ADR: Type:

A (Augmented)	D (Delayed)
B (Bizarre)	E (Ending Use)
C (Continuous)	F (Failure of Efficacy)

Type A reactions (augmented)

1. These ADR **are expected**
2. They can be **predicted** on the base of pharmacodynamic properties of drug
3. They depend **on drug dose**, they appear at higher doses
4. Frequency is **high <u>≥ than 1%</u>**
5. **mortality is low**
6. Therapy consists **in dose adjustment**
    a. *e.g.:* cough after ACEI, bleeding from GIT after NSA, aspirin, corticoids ...

Type B reactions (bizarre)

1. Idiosyncratic reactions
2. These ADR are not expected
3. They can be hardly predicted
4. Doesn´t depend on dose
5. Frequency is low < than 0,1%
6. Mortality is high
7. Treatment consists in stopping drug administration e.g.: haemolytic anaemia after metyldopa,
    a. hepatitis induced by isoniazid, allergic reaction after PNC.

Type C (continous)

- This type of ADR increases number of **"spontanneous" diseases**
- They occur usually after **long-lasting administration**
- They are often **serious and persistant**
- **Mechanism of** genesis **is unclear**
- They are **unexpected**, not predictable
- They can´t be verified experimentally
- *e.g.:* oral contraceptives and increased occurrence of thromboembolia, analgetic nephropaty

Type D (delayed)

- Late ADR (years resp. generations)
- Teratogenity
- Carcinogenity
- Mutagenity
- *e.g.:* ca. of vagina at daughters of mothers treated with dietylstilbestrol

Type E (End of use)

- After therapy ending (syndrom from omitting)
- Rebound phenomenon
- *e.g.:* beta blockers, opioids, corticosteroids, nitrates ...
-

Severity of reaction

Mild: - Bothersome but requires no change in therapy

Moderate: - Requires change in therapy, additional treatment, hospitalization

Severe: - Disabling or life-threatening.

Serious ADR

- Result in death
- Life-threatening
- Require hospitalization
- Prolonged hospitalization
- Cause disability
- Cause congenital anomalies
- Medically significant
-

Observed ADR: - a reaction that is “directly observed or occurring while the patient was on the suspected causative agent.”

Historical ADC: - “Historical” generally refers to events in the past (i.e., more than 3 months old) or that reportedly occurred in the past at another healthcare setting.

Lecture Note		
Subject: Ph.Cology, 404T	**SEM-4th**	**UNIT-V**
Submitted By:	**Prasenjit Mishra**	**HCP-345-BBSR**

ANTIANXIETY

Anxiety is Physical and emotional distress which interfere with normal life.

Symptoms of anxiety

- Psychic or emotional state.
- Somatic or physical symptoms.

Common Emotional Symptoms of anxiety are

- irrational and excessive fear and worry
- Irritability
- Restlessness
- Trouble concentrating
- Feeling tense

Common Physical Symptoms of Anxiety

Sweating Tachycardia Stomach upset Shortness of breath Frequent urination or diarrhea Sleep disturbances (Insomnia) Fatigue

Types of anxiety

1. Generalized anxiety disorder
2. Post-traumatic stress disorder (PTSD).
3. Obsessive-compulsive disorder (OCD).
4. Panic disorder
5. Phobia

Generalized Anxiety Disorder (GAD):-Patients are usually and constantly worried about health, money, work with no apparent reasons.

Post-traumatic stress disorder (PTSD):- An anxiety disorder that affects people who have experienced a severe emotional trauma, such as rape or dramatic car accident, or even war.

Obsessive-Compulsive Disorder (OCD):- An anxiety disorder in which people cannot prevent themselves from unwanted thoughts or behaviors that seem impossible to stop as washing their hands

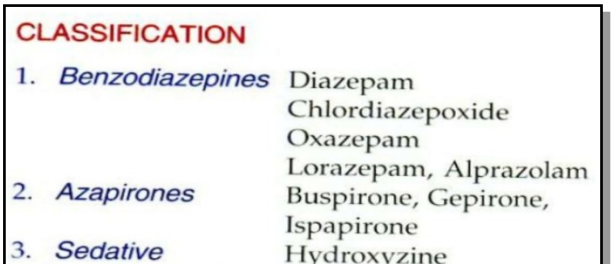
Panic disorder:- An disorder in which people have sudden and intense attacks of anxiety in certain situations.

Phobia An intense, uncontrolled fear of a specific situation such as open spaces & heights

Treatment 0f Anxiety

- Psychotherapy (cognitive behavioral therapy).
- Anxiolytics

Anti anxiety drugs:- Mild CNS depressants , aimed to control the symptoms of anxiety , produces a restful state of mind without interfering with normal mental or physical function classification.



4.	β blocker	Propranolol

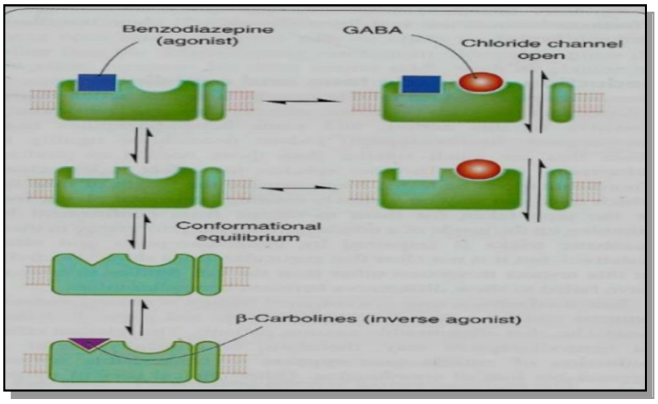
Classifications of Benzodiazepines –

Short acting: (3-5 hours): triazolam –

Intermediate: (6-24 hours) Alprazolam Lorazepam Oxazepam Estazolam Temazepam

Long acting: (24-72 hours) Clonazepam Chlordiazepoxide Diazepam Flurazepam

Mechanism of Action:- Benzodiazepines act by binding to BZ receptors in the brain which enhance GABA((γ-aminobutyric acid): is an inhibitory neurotransmitter) action on brain through chloride channels opening increasing chloride influx to the cell then hyper- polarization lead to inhibition of brain.



Pharmacokinetics • are lipid soluble • well absorbed orally, • can be given parenterally • Chlordiazepoxide- Diazepam -widely distributed. • cross placental barrier (in Fetal depression). • excreted in milk (neonatal depression).

metabolized in the liver to active metabolites Redistribution from CNS to skeletal muscles, adipose tissue.

Pharmacological Actions

- Anxiolytic action.
- Depression of cognitive and psychomotor function
- Sedative & hypnotic actions
- Anterograde amnesia.
- Minimal depressant effects on – Cardiovascular system – Respiratory system
- Some have anticonvulsant effect: – clonazepam, diazepam.

Therapeutic Uses

Anxiety disorders: short term relief of severe anxiety General anxiety disorder Obsessive compulsive disorder Panic attack with depression Alprazolam (antidepressant effect)

Sleep disorders (Insomnia). – Triazolam, Lorazepam, Flurazepam

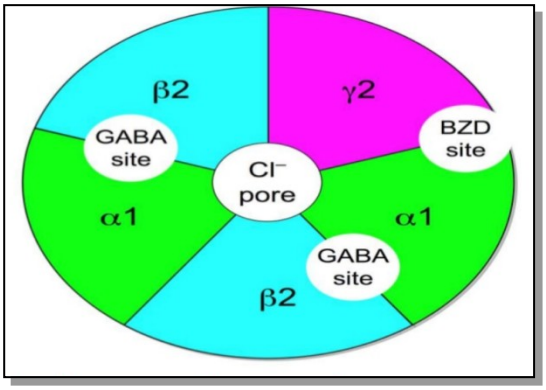
Treatment of epilepsy Diazepam – Lorazepam

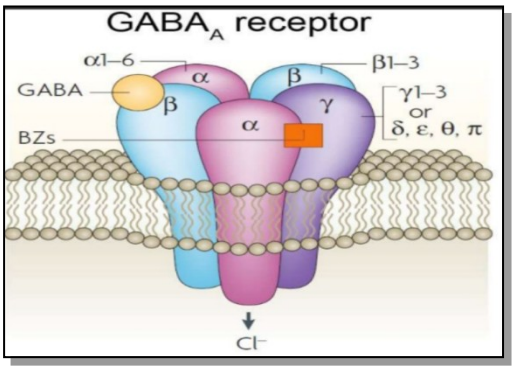
In anesthesia

- Preanesthetic medication (diazepam).
- Induction of anesthesia (Midazolam, IV)

Adverse Effects

- Ataxia (motor incoordination)
- Cognitive impairment.
- Hangover: (drowsiness, confusion)
- Tolerance & dependence
- Risk of withdrawal symptoms Rebound Insomnia, anorexia, anxiety, agitation, tremors and convulsion.
- Toxic effects: respiratory & cardiovascular depression in large doses.





Flumazenil:- Rapidly reverse effects of BZD , can cause withdrawal syndrome in patients getting BZD . Orally effective. Also given IV

Uses:- 1. BZD poisoning 2. Reversal of BZD induced anesthesia

Adverse effects – agitation, discomfort, anxiety,coldness & withdrawal seizures.

Drug interactions

CNS depressants:- Alcohol & Antihistaminics increase the of effect of benzodiazepines

Cytochrome P450 (CYT P450) inhibitors:- Cimetidine & Erythromycin increase the t ½ of benzodiazepines

CYT P450 inducers :-Phenytoin & Rifampicin decrease the t 1/2 of benzodiazepines.

Dose should be reduced in o Liver disease o Old people. Precaution Should not used in • pregnant women or breast-feeding. • People over 65.

5HT1A agonists Buspirone:-

- acts as agonist at brain 5HT1A receptors
- rapidly absorbed orally.
- Slow onset of action (delayed effect)
- T½ : (2 – 4 h).
- liver dysfunction decrease its clearance.

Drug Interactions with CYT P450 inducers and inhibitors.

USE • Only anxiolytic • No hypnotic effect. • Not muscle relaxant. • Not anticonvulsant. • No potentiation of other CNS depressants. • Minimal psychomotor and cognitive dysfunctions. • Does not affect driving skills. • Minimal risk of dependence. • No withdrawal signs.

BETA BLOCKERS **Propranolol – atenolol**

- Act by blocking peripheral sympathetic system.
- Reduce somatic symptoms of anxiety.
- Decrease BP & slow HR.

Used in social phobia. • are less effective for other forms of anxiety

HYDROXYZINE – An H1 antihistaminic with sedative, antiemetic, antimuscarinic and spasmolytic properties.

Hydroxyzine used in reactive anxiety or that associated with marked autonomic symptoms.
It is useful in pruritus and urticaria.

Note:-

General anxiety disorder therapy of GAD include a combination of BDZ, SSRI and cognitive behavioral therapy.
Some patients will need maintenance drug therapy almost life long.
short course of BZD – lowest dose & on as needed basis. Not > 4-6 wks. Short acting fast but day time anxiety and difficult to withdraw. Long acting sedation problem, slow withdrawal easier.

Buspirone – adv non sedating,but slow , effective in head injury & dementia pts.
• SSRIs & SNRIs – effective in anti depressant dose.
• Anti convulsants – gabapentine,tiagabine etc.

Obsessive Compulsive Disorder – • 50- 60% pts show improvement with only pharmacotherapy. • Clomipramine – (50-150mg/d) • Fluoxetine(5-60mg/d) • Fluvoxamine(25-

300mg/d) • Sertraline(50-150mg/d) • CBT (cognitive behaviour therapy) • Deep brain stimulation

Lecture Note		
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ANTIDEPRESSANTS

.**Depression**

Major depression and mania are two extremes of affective disorders which refer to a pathological change in mood state.

The symptoms of depression are intense feelings of sadness, hopelessness, and despair as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

Mania is characterized by the opposite behavior: enthusiasm, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

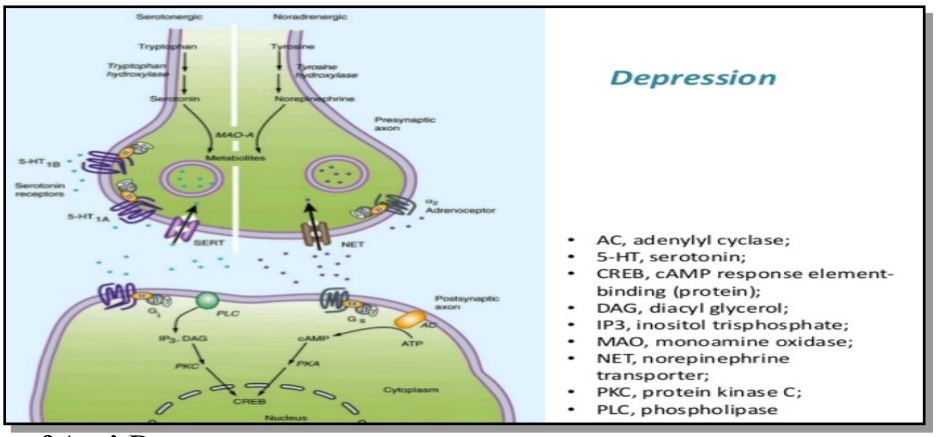
Types of Depression

- Major depression
- Chronic depression (Dysthymia)
- Atypical depression
- Bipolar disorder/Manic depression
- Seasonal depression (SAD)

Mechanism of Depression/ Hypothesis

Depression is associated with changes in the level of neurotransmitters signaling in the brain that (or both) with significant downstream effects which help nerve cells to communicate.
E.g Serotonin, Dopamine, Nor-epinephrine.

The level can be influenced by physical illness, genetics, substance abuse, diet, hormonal changes, brain injuries or social circumstances.



Classification of Anti-Depressant:

a. **Reversible inhibitors of MAO-A (RIMAs):** Moclobemide, Clorgyline
b. **Tricyclic antidepressants (TCAs):**
    i. **NA + 5-HT reuptake inhibitors:** Imipramine, Amitriptyline, Trimipramine, Doxepin, Dothiepin, Clomipramine
    ii. **Predominantly NA reuptake inhibitors**: Desipramine, Nortriptyline, Amoxapine, Reboxetine
    iii. **Selective serotonin reuptake inhibitors (SSRis):** Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram
c. **Atypical antidepressants:** Trazodone, Mianserin, Mirtazapine, Venlafaxine, Duloxetine, Tianeptine, Amineptine, Bupropion
d. **5-HT2Antagonists:** Trazodone and Nefazodone

MAO inhibitors

MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT). Two isoenzyme forms of MAO have been identified. Dopamine is degraded equally by both isoenzymes.

MOA isoenzyme	Active against	Inhibited by
MAO-**A**	5HTans NA	Clorgyline Moclobemide
MAO-**B**	Phenylethlamine	Selegiline

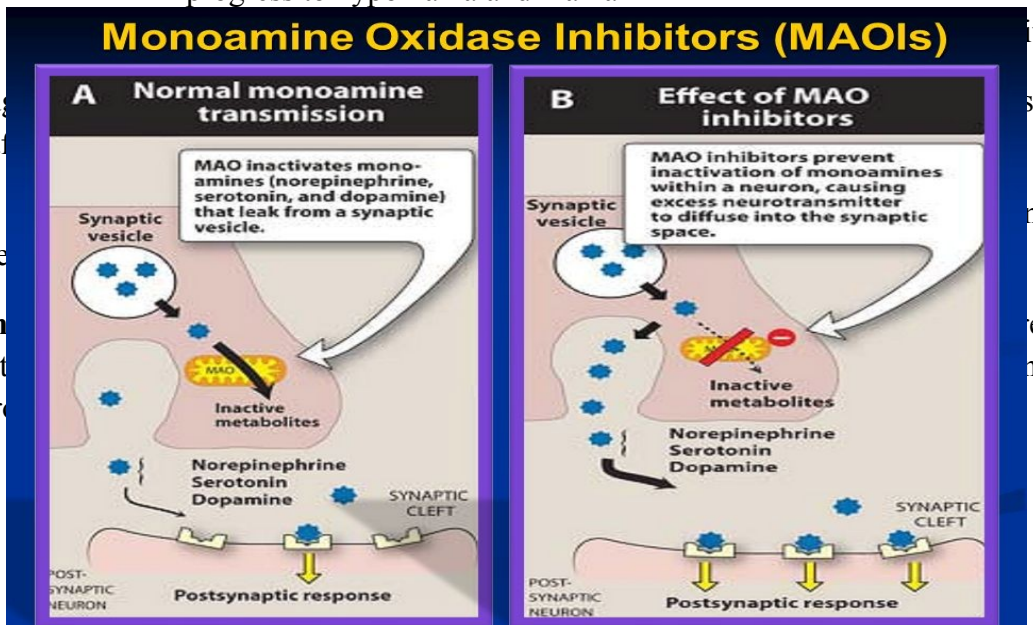
MAO inhibitors (MAOIs) inactivate MAO, permitting neurotransmitter molecules to accumulate within the presynaptic neuron and leak into the synaptic space causing activation of norepinephrine and serotonin receptors.

MOA inhibitors inhibit the metabolism of biological amines to cause disproportionate elevation of mood.

MAO inhibitors:- Isocarboxazid ✹ Phenelzine ✹ Tranylcypromine ✹ Selegiline

The nonselective MAO inhibitors causes

- elevate the mood in depressed patients
- progress to hypomania and mania



ividuals .

The drug st for 2-3 weeks af

• MOA ne levels remain e

Mechan eversible inactivat ne within the neur

Interactions: MAO inhibitors inhibit a number of other enzymes as well, and interact with many food constituents and drugs.These drugs also inhibit MAO in the liver and gut that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods causing a high incidence of drug-drug and drug-food interactions ◦ Selegiline may produce less inhibition of gut.

- ***Cheese reaction:*** MAO inhibiters indirectly acting sympathomimetic amines escape degradation in intestinal wall and liver reaching into systemic circulation they displace large amounts of NA from transmitter loaded adrenergic nerve endings hypertensive crisis, cerebrovascular accidents. Alpha blockers (e.g.: phentolamine, prazosin) or chlorpromazine can be used for treatment of chees reaction.
- Cold and cough remedies: Cough syrup contains ephedrine or other sympathomimetics cause hypertensive reaction.
- Reserpine, guanethidine, tricyclic antidepressants: Excitement, rise in BP and body temperature can occur when given these drugs to patient on MOA inhibitor (due to NA release or uptake blocking action).
- Levodopa: Excitement and hypertension, due to increase in biological half life of DA and NA.
- Antiparkinsonian anticholinergics: Hallucinations and symptoms similar to those of atropine poisoning occur. – Barbiturates, alcohol, opioids, antihistamines: respiration may fail.
- Pethidine: High fever, sweating, excitation, delirium, convulsions, and severe respiratory depression may occur.

Reversible inhibitors of MAO-A

Moclobemide It is reversible and selective MAO-A inhibitor with short duration of action and full MAO activity is restored within 1-2 days of stopping the drug. Its effective antidepressant,

comparable to TCAs. It lacks the anticholinergic, sedative, cognitive, psychomotor and cardiovascular adverse effects of typical TCAs and is safer in overdose.

ADR: nausea, dizziness, headache, insomnia, rarely excitement and liver damage.

Use: Alternative for TCAs for mild to moderate depression and social phobia.

Dose: 150 mg; BD or TID (Max 600 mg/ kg/ day).

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Imipramine	Maprotiline
Clomipramine	Nortriptyline
Desipramine	Protriptyline
Trimipramine	Amoxapine
Amitriptyline	Doxepin

Imipramine: - It is an analogue of CPZ and found during clinical trails to selectively benefit depressed but not agitated psychotics.

MOA: – TCAs block norepinephrine and serotonin reuptake into the neuron.

Inhibition of neurotransmitter reuptake: TCAs is potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. At therapeutic concentrations, they do not block dopamine transporters. TCAs cause increased concentrations of monoamines in the synaptic cleft, ultimately resulting in antidepressant effects. Maprotiline and desipramine are relatively selective inhibitors of norepinephrine reuptake.

Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. It is not known if any of these actions produce TCAs' therapeutic benefit.

Pharmacological action: • Central nervous system

:

Normal individual	Depressed patient
It induces a peculiar clumsy feeling, tiredness, light- headedness, sleepiness, difficulty in concentrating and thinking, unsteady gait, anxiety. no mood elevation or euphoria.	Little acute effects are produced, except sedation. After 2-3 weeks of continuous treatment, the mood is gradually elevated, patients become more communicative and start taking interest in self and surroundings

ANS: Most TCAs are potent anticholinergics-cause dry mouth, blurring of vision, constipation and urinary

CVS: Effects on cardiovascular function are prominent, occur at therapeutic concentrations and may be dangerous in overdose.

i. Tachycardia: due to anticholinergic and NA potentiating actions.
ii. Postural hypotension: due to inhibition of cardiovascular reflexes and α1 blockade.
iii. ECG changes and cardiac arrhythmias: T wave suppression or inversion is the most consistent change.
iv. Arrhythmias occur in overdose due to interference with intraventricular conduction, combination of NA potentiating + ACh blocking actions and direct myocardial depression.

Tolerance and dependence:

• Tolerance to the anticholinergic and hypotensive effects of imipramine-like drugs develops gradually, though antidepressant action is sustained.

• Psychological dependence on these drugs is rare, because their acute effects are not pleasant.

Acute poisoning:

• Poisoning with TCA is frequent and cause excitement, delirium, and other anticholinergic symptoms as seen in atropine poisoning.

Treatment for acute TCA poisoning: Gastric lavage, respiratory assistance, fluid infusion, maintenance of BP and body temperature. Diazepam may be given i.c. to control convulsion and delirium and to prevent cardiac arrhythmias, propranolol/ lidocaine may be used.

Pharmacokinetics:

a. TCAs are well absorbed upon oral administration. Because of their lipophilic nature, they are widely distributed and readily penetrate into the CNS (t1/2 is 4 to 17 hours for imipramine).
b. As a result of their variable first-pass metabolism in the liver, dosage adjustment may require at the initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced to improve tolerability, unless relapse occurs.
c. These drugs are metabolized by the hepatic microsomal system and conjugated with glucuronic acid. TCAs are excreted as inactive metabolites via the kidney.

Adverse effects:

a. Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of narrow-angle glaucoma.
b. The TCAs also block α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia.

c. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction, as evidenced by erectile dysfunction in men and anorgasmia in women, occurs in a significant minority of patients, but the incidence is still considered to be lower than the incidence of sexual dysfunction associated with the SSRIs.

Selective Serotonin Reuptake Inhibitors (SSRis):-

The major limitations of conventional TCAs are:

a. Frequent anticholinergic, cardiovascular and neurological side effects.
b. Relatively low safety margin, hazardous in overdose; fatalities common.
c. Lag time of 2-4 weeks before antidepressant action manifests.
d. Significant number of patients respond incompletely and some do not respond.
e. The selective serotonin reuptake inhibitors (SSRIs) are inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter.
f. SSRIs also have little blocking activity at muscarinic, α-adrenergic, and histaminic H1 receptors.
g. The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity.
h. SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.

Pharmacokinetics

a) All SSRI are well absorbed after oral administration.
b) Food has little effect on absorption (except sertraline, for which food will increase its absorption).
c) Majority of SSRIs have plasma half –lives that range of 16-36 h.
d) Metabolism by cytochrome P450 (CYP450)-dependent enzymes and glucuronide or sulfate conjugation occur extensively.
e) SSRIs may affect the metabolism of multiple medications and its excretion of the SSRIs is primarily through the kidneys, except for paroxetine and sertraline, which also undergo fecal excretion (35 and 50 percent, respectively).
f) Dosages of all of these drugs should be adjusted downward in patients with hepatic impairment.
g) Fluoxetine differs from the other members of the class in two respects. First, it has a longer half-life (50 hours) and is available as a sustained-release preparation allowing once-weekly dosing.
h) Second, the metabolite of the S-enantiomer, S-norfluoxetine, is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days.

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Therapeutic uses

a. The primary indication for SSRIs is depression, for which they are as effective as the TCAs. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder and premenstrual dysphoric disorder.
b. Fluoxetine is approved for Bulimia nervosa.
c. Fluoxetine, sertraline, and fluvoxamine are approved for use in children to treat obsessive-compulsive disorder, and fluoxetine is approved to treat childhood depression by US-FDA.

Adverse effects

a. SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs. • SSRIs are commonly cause headache, sweating, anxiety and agitation, gastrointestinal effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight and sleep disturbances (insomnia and somnolence).
b. Sleep disturbances: Paroxetine and fluvoxamine are generally more sedative than other SSRI. Can be used as antidepressant.
c. Sexual dysfunction: Loss of libido, delayed ejaculation, and anorgasmia are underreported side effects. In men with erectile dysfunction and depression, treatment with sildenafil, vardenafil, or tadalafil may improve sexual function.

Caution :-***Use in children and teenagers:*** **–** Antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 children report suicidal ideation as a result of SSRI treatment.

– Pediatric patients should be observed for worsening depression and suicidal thinking whenever any antidepressant is started or its dose is increased or decreased.

Overdoses:

a. Large intakes of SSRIs do not cause cardiac arrhythmias (compared to the arrhythmia risk for the TCAs), but seizures are a possibility because all antidepressants may lower the seizure threshold.
b. All SSRIs have the potential to cause a serotonin syndrome that may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs when used in the presence of a MAOI or other highly serotonergic drug.
c. Therefore, extended periods of washout for each drug class should occur prior to the administration of the other class of drugs.

Discontinuation syndrome:

a. All SSRIs have the potential for causing a discontinuation syndrome after their abrupt withdrawal, the agents with the shorter half-lives and having inactive metabolites have a higher risk for such an adverse reaction.
b. Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome.
c. Possible signs and symptoms of such a serotonin-related discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

ATYPICAL ANTIDEPRESSANTS

They are a mixed group of agents that have actions at several different sites.

Atypical antidepressants ease depression by affecting chemical messengers (neurotransmitters) used to communicate between brain cells.

Like other types of antidepressants, atypical antidepressants affect neurotransmitters including dopamine, serotonin and nor epinephrine.

Changing the balance of these chemicals seems to help brain cells send and receive messages, which in turn boosts mood.

Atypical antidepressants are:- Bupropion ,Mirtazapine, Nefazodone, Trazodone

Bupropion

Weak dopamine and norepinephrine reuptake inhibitor ✹ Bupropion also assists in decreasing the craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking ✹ Can help with cocaine withdrawal ✹ Side effects ◦ Dry mouth ◦ Nervousness ◦ Tremor ◦ Increased risk for seizures at high doses

Mirtazapine

Enhances serotonin and norepinephrine neurotransmission by blocking presynaptic α2 receptors and 5-HT2 receptors ✹ It is a sedative because of its potent antihistaminic activity ✹ No antimuscarinic side effects ✹ No interference with sexual functioning ✹ Side effects ◦ Increased appetite and weight gain ◦ Marked sedation

Trazodone:

a. It is the first atypical antidepressant; selectively but less efficiently blocks 5-HT uptake and has prominent a blocking as well as weak 5-HT2 antagonistic action.
b. It is not anticholinergic, but causes bradycardia, and doesn't interfere with intracardiac conduction, hence it is less prone to cause arrhythmia.
c. trazodone is well tolerated and relatively safe in overdose: seizures do not occur. Its t1/z is short (approx. 6 hr).

d. ADR: Inappropriate, prolonged and painful penile erection (priapism) occurs in few recipients resulting in impotence.

Mianserin:-not inhibiting either NA or 5-HT uptake; but blocks presynaptic alpha 2 receptors
Tianeptine:-This antidepressant is reported to increase rather than inhibit 5-HT uptake, and is neither sedative nor stimulant.

Amineptine

i. Enhances 5-HT uptake
ii. It produces anticholinergic side effects including tachycardia, confusion and delirium.
iii. Postural hypotension, conduction disturbances and arrhythmias can occur, especially in patients with heart disease.

Venlafaxine:-A novel antidepressant referred to as 'serotonin and noradrenaline reuptake inhibitor' (SNRI)

USES

i. (major) depression
ii. Obsessive-compulsive and phobic status
iii. Anxiety disorders
iv. Neuropathic pain
v. Attention deficit-hyperactivity disorder in children
vi. Enuresis
vii. Migraine
viii. Pruritus

Lecture Note		
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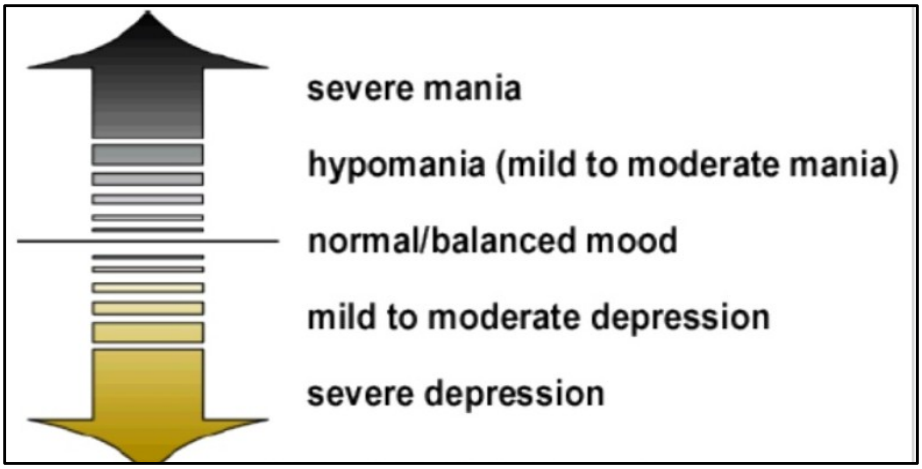
ANTIMANIC DRUGS

Mania is characterized by excessive desire & too much of euphoria

Majority of the patients of mania also experience cyclic episodes of mania followed by depression

Patients suffer episodes of mania, hypomania & depression, classically with period of normal mood in between.



Classification of drugs

- Lithium
- Carbamazepine
- Valproic acid
- Lamotrigine
- Olanzapine

LITHIUM

Lithium is small monovalent cation.

Pharmacokinetics :–

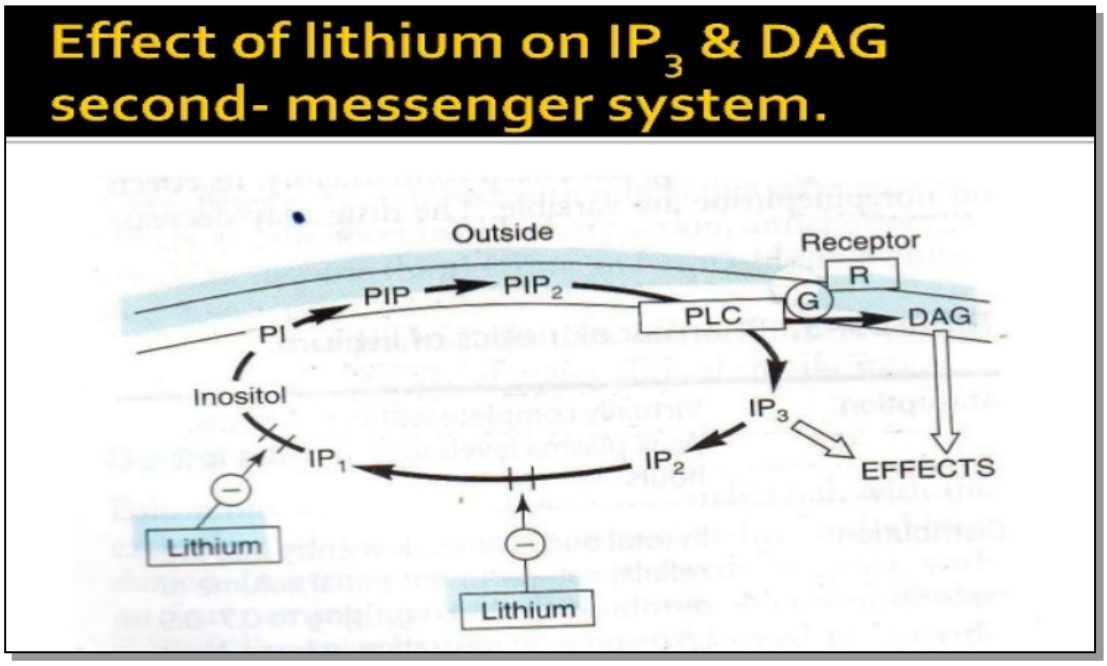
- Given orally rapidly absorbed from gut
- Lithium enters cells about as readily as sodium but does not leave as readily(mechanism uncertain)

- Being a metallic ion not metabolized, nor is it bound to plasma protein
- Only kidney eliminates lithium. Like sodium it is filtered by glomerulus & 80% reabsorbed by proximal tubule not reabsorbed in distal tubule.
- A steady plasma concentration will attained after about 5-6 days in patients with normal renal function
- Half life – 15-30 hrs.
- Lithium margin of safety is narrow
- Monitoring serum Li concentration is essential for optimal therapy & measured 12 hr after last dose to reflect steady concentration. 9. 0.5-0.8 mEQ/L - for maintenance therapy 0.8- 1.1 mEQ/L - for episode of mania.
- Toxic symptom occur >1.5 mEQ/L. Salivary concentration is propionate to serum concentration may be used to non invasive monitoring. Lithium is secreted to breast milk & cross placenta.

MOA-

CNS:-Prolonged administration acts as mood stabilizer in bipolar disease. In acute mania, it gradually suppress episode taking 1-2 week; continued T/t prevent cyclic mood changes.

- Lithium by inhibits several important enzyme in conversion of IP 2 to IP 1 & conversion of IP to inositol.
- Causes depletion of second messenger source PIP2 (phosphatidyl inositol biphosphate) & therefore reduce release of IP3 & DAG & its effects (activation of protein kinase c , mobilization of intracellular ca 2+).
- Before therapy, such activity might be greatly increased in mania. Lithium could cause a selective depression of overactive circuits.
- IP3 & DAG important second messenger of adrenergic & muscarinic transmission
- Li inhibits action of ADH on distal tubule & causes Polyuria (diabetes insipidus like state) , Leukocyte count increased by li therapy , Lithium reduces thyroxine synthesis (sub clinical hypothyroidism)



Adverse effect:

- Toxicity occur at levels only marginaly higher then therapeutic levels.
- Nausea, vomiting & mild diarrhoea, minimized by starting at lower dose .
- Thirst & polyuria occur to most of them
- Fine tremor & rarely seizure are seen at therapeutic dose.

CNS toxicity:- when plasma concentration rise

- Coarse tremor, giddiness, ataxia , motor incoordination.
- Over dose symptom above 2 meq/L

Acute intoxication - muscle twitching, drowsiness, delirium, coma & convulsion. ***Treatment*** is symptomatic, osmotic diuretic & sodium bicarbonate infusion promote Li excretion

Long term use develop renal diabetes insipidus , goiter has been reported in 4% cases.

Lithium is contraindicated during pregnancy, may produce foetal goiter & other cardiac abnormality.

Drug Interaction

- Diuretics (Thiazide, Furosemide) by causing Na + loss promote proximal tubular reabsorption of Na + as well as Li
- Plasma level of Li rises.
- Li tends to enhance insulin / sulfonylurea induced hypoglycemia.
- Neuroleptics , Phenothiazines & Butyrophenone combination produces marked tremor & rigidity.
- Except Paracetamol or Aspirin other NSAID'S reduces renal clearance of Li+
- Li+ paradoxically potentiates succinylcholine or d-tubocurarine induced muscle relaxation

  USE:

  Li used as carbonate salt because less hygroscopic & less gastric irritant than Licl.

  Dose – started at 600mg /day & increased up to therapeutic plasma level in dose of 600 -1200 mg/day.

Acute manic episode – Acute phase most preferred neuroleptic generally by IM route (Haloperidol) with or without diazepam

- Li is not used in acute phase due to slower response
- After the episode under control , maintenance therapy given for 6-12 month to prevent recurrence.
- Prophylaxis in bipolar disorder – Proven efficacy in bipolar disorder maintained at plasma concentration 0.5-0.8 meq/L
- Benefit & risk are to be weighed in individual cases.

In unipolar depression – combination of antidepressant + Li can be used initially & Li alone is continued in the maintenance phase.

Used in clusture headache

Leucocyte count increases with Li+ therapy Useful for cancer chemotherapy induced leukopenia & agranulocytosis

Carbamazepine

Alternative for lithium for prophylaxis of bipolar disorder

Stronger support its used in treatment of mania.

Combined with Li Relapse & more prone to rapid cycling mood state.

Dosage –200 mg twice daily with increase needed, maintenance dosage 800 mg – 1200mg/day,plasma concentration 3-14 mg /ml.

Sodium valporate

Efficacy in prevention & treatment of acute mania

On set Action is faster than Li & useful not responding to Li or CBZ or not tolerating.

A combination with Li effective in resistant to monotherapy with either drug.

Starting dose 750 mg/day, increasing rapidly up to 1500 –2000 mg.

Atypical

Olanzapine for acute mania & show efficacy in bipolar illness.

Because Olanzapine low risk of EPS & agraulocytosis

used as adjuvant / alternative to LI .

Alternatively Risperidone & Queitiapine can also be used

New Molecules

- Topiramate
- Gabapentin
- lamotrigine

- Mood elevation has been noticed during antiepileptic use
- Lamotrigine is found to be useful in MDP
- Carries minimum risk of inducing mania

Lecture Note		
Subject: Ph.Cology, 404T	**SEM-4th**	**UNIT-V**
Submitted By:	**Prasenjit Mishra**	**HCP-345-BBSR**

ANTIPSYCHOTIC DRUGS

• Antipsychotic drugs ***(also called neuroleptics or major tranquilizers***) are used primarily to treat schizophrenia (a biologic illness), but they are also effective in other psychotic states, including manic states with psychotic symptoms such as grandiosity, paranoia, and hallucinations, and delusions.

• Antipsychotic drugs are not curative and do not eliminate the chronic thought disorder, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

History of antipsychotic drugs

• Antipsychotic drugs have been used in Western medicine for more than 50 years.

• Chlorpromazine (1952) and Reserpine were the first drugs found to be useful in schizophrenia.

• Tricyclic and MOA inhibitor antidepressant in 1957-58.

• Major novel antipsychotics are selective serotonin reuptake inhibitor and it has been introduced in 1980s.

• Little attention was paid to Cade's report in 1949 that Lithium could be used for excitement and mania: its effective use started in the 1960s and now it has a unique place in psychiatry.

Psychoses These are severe psychiatric illness with serious distortion of thought, behaviour, capacity to recognise reality and of perception (delusions and hallucinations). There is inexplicable misperception and misevaluation; the patient is unable to meet the ordinary demands of life.

Types:

- Acute and chronic organic brain syndromes (cognitive disorders)
- Functional disorders (Schizophrenia, Paranoid states)
- Mood (affective) disorders (Mania Depression)

Acute and chronic organic brain syndromes

– Delirium and dementia.

– Cases: Exposure to toxic substances or pathological changes.

– Prominent features are confusion, disorientation, defective memory and disorganized behaviour.

• Functional disorders

– Causes: No underlying cause can be defined.

– Memory and orientation are mostly retained but emotion, thought, reasoning and behaviour are seriously altered. Psychoses

Schizophrenia is a particular type of psychosis (that is, a mental disorder caused by some inherent dysfunction of the brain).

It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. This mental disorder is a common affliction, occurring in about 1 percent of the population.

Paranoid states with marked persecutory or other kinds of fixed delusions (false beliefs) and loss of insight into the abnormality. Psychoses - Schizophrenia and Paranoid states.

Psychoses - Affective disorders

• **Mania-** elation or irritable mood, reduced sleep, hyperactivity, uncontrollable thought and speech, may be associated with reckless or violent behavior,

• **Depression-** sadness, loss of interest and pleasure, worthlessness, guilt, physical and mental slowing, melancholia, self-destructive ideation.

• A common form of mood disorders is bipolar disorder with cyclically alternating manic and depressive phase. The relapsing mood disorder may be unipolar (mania or depression) with waxing and waning course.

Neuroses • less serious, depending on the predominant feature

– **Anxiety** (unpleasant emotional state with worry, tension)

– **Phobic** states (fear of unknown)

– **Obsessive-compulsive disorder** (limited abnormality of through or behaviour)

– **Reactive depression** (due to physical illness, loss, blow to self-esteem or bereavement)

– **Post-traumatic stress disorder** (varied symptoms following distressing experiences like war, riots, earthquakes, etc.) – Hysterical (Dramatic symptoms resembling serious physical illness).

PHARMACOLOGICAL CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

FIRST-GENERATION ANTIPSYCHOTIC **(low potency)**

• Chlorpromazine • Prochlorperazine • Thioridazine

FIRST-GENERATION ANTIPSYCHOTIC **(high potency)**

• Fluphenazine • Haloperidol • Pimozide • Thiothixene

SECOND GENERATION ANTIPSYCHOTIC • Aripiprazole • Asenapine • Clozapine • Iloperidone • Lurasidone • Olanzapine • Quetiapine • Paliperidone • Risperidone • Ziprasidone

CHEMICAL CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

a) **Phenothiazines**: • Aliphatic side chain: Chlorpromazine, triflupromazine • Piperidine side chain: Thioridazine • Piperazine side chain: Trifluoperazine, fluphenazine

b) **Butyrophenones:** Haloperidol, Trifluperidol, Penfluridol

c) Thioxanthenes: Flupenthixol – Other heterocyclics: Pimozide, Loxapine

d)**Atypical antipsychotics:** Clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone

Pathophysiology of mental illness is not clear, it maybe dopaminergic **over activity** in the limbic system (schizophrenia and mania), deficit in monoamines [NA, 5-HT] (depression).

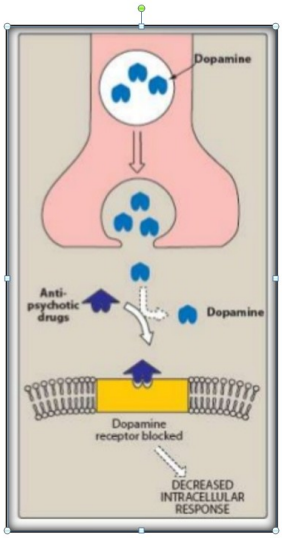
Treatment is empirical, symptom oriented and not disease specific. Depending on the primary use, the psychotropic drugs may be grouped into: – Anti-psychotic – Anti manic – Antidepressants – Antianxiety – Psychotomimetic Pharmacotherapy of metal illness

• **First-generation antipsychotics** • The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of D2 dopamine receptors. • First-generation antipsychotics are more likely to be associated with movement disorders, particularly for drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol. Pharmacotherapy of metal illness

• **Second-generation antipsychotic drugs** • The second generation antipsychotic drugs (also referred to as "atypical" antipsychotics) have fewer extrapyramidal symptoms (EPS) than the first-generation agents, but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight

gain. • The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine receptors. Pharmacotherapy of metal illness

Pharmacology of chlorpromazine (CPZ)



•– Dopamine receptor–blocking activity in the brain:

All of the first generation and most of the second- generation

antipsychotic drugs block dopamine receptors in the brain and

the periphery (except clozapine-like atypical).

The clinical efficacy of the typical antipsychotic drugs correlates

closely with their relative ability to block D2 receptors in the mesolimbic

system of the brain.

Pharmacology of chlorpromazine (CPZ)

• **Mechanism of action** – The actions of the antipsychotic drugs are antagonized by agents that raise synaptic dopamine concentrations (for example, levodopa and amphetamines, bromocriptine) or mimic dopamine at post-synaptic binding sites. – Dopaminergic blockade pituitary locatotropes cause the hyperprolactinemia, while that in CTZ is responsible for antiemetic action.

Chlorpromazine is a prototype agent for typical antipsychotic agent.

➢ **CNS:** Effects differ in normal and psychotic individuals • In normal individual CPZ indifference to surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep. Spontaneous movements are minimized but slurring of speech, ataxia or motor incoordination does not occur. • In normal individuals CPZ produces neuroleptic syndrome, and is quite different from the sedative action of barbiturates. • In CPZ reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology. Disturbed thought and behaviour are gradually normalized, anxiety is relieved. • Hyperactivity, hallucinations and delusions are suppressed. • All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective doses.

• The sedative effect is produced promptly, while antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect. – Extrapyramidal motor disturbances are intimately linked to the antipsychotic effect, but are more prominent in the high potency compounds and least

in thioridazine, clozapine and other atypical antipsychotics. – Chlorpromazine lowers seizure threshold and can precipitate fits in untreated epileptics. – Temperature control is knocked off at relatively higher doses.

- **ANS:** – ANS effect of antipsychotic agents are complex and unpredictable. Neuroleptics have varying degree of alpha adrenergic blocking activity. Chlorpromazine, clozapine, and thioridazine have particularly significant alpha adrenergic antagonistic activity. – phenothiazines have weak H1-antihistaminic and anti-5-HT action. • Effects on Sleep: Antipsychotic drugs have inconsistent effects on sleep patterns but tend to normalize sleep disturbances characteristic of many psychoses and mania.
- **Local anaesthetic:** Chlorpromazine is as potent a local anaesthetic as procaine. Because of its irritation action CPZ is not used for this purposes and also its having weaker/ no membrane stabilizing action. • Cardiovascular System: – Chlorpromazine has complex actions on the cardiovascular system, directly affecting the heart and blood vessels and indirectly acting through CNS and autonomic reflexes. – Chlorpromazine and less potent antipsychotic agents, as well as reserpine, risperidone, and olanzapine, can cause orthostatic hypotension. – Partial tolerance develops after chronic use. Reflex tachycardia accompanies hypotension. Arrhythmia may occur in overdose especially with thioridazine.
- **Skeletal muscle:** Neuroleptics have no effect on muscle fibers or neuromuscular transmission. They reduce certain types of spasticity : the site of action being in the basal ganglia or medulla oblongata. Spinal reflex are not affected. • Kidney and Electrolyte Balance: Chlorpromazine may have weak diuretic effects in animals and human beings because of a depressant action on the secretion of vasopressin (antidiuretic hormone), inhibition of reabsorption of water and electrolytes by a direct action on the renal tubule, or both.
- **Endocrine: –** Neuroleptics consistently increase prolactin release by blocking the inhibitory action of DA on pituitary lactotropes. This may result in galactorrhoea and gynaecomastia. They reduce gonadotropin secretion, but amenorrhoea and infertility occur only occasionally. – ACTH release in response to stress is diminished- corticosteroid levels fail to increase under such circumstances. Release of GH is also reduced but this is not sufficient to cause growth retardation in children or to be beneficial in acromegaly. – Decreased release of ADH may result in an increase in urine volume. A direct action on kidney tubules may add to it, but Na+ excretion is not affected.
- **Pharmacokinetics: –** Some antipsychotic drugs have erratic and unpredictable patterns of absorption after oral administration. – Parenteral (intramuscular) administration increases the bioavailability of active drug four- to ten fold. – Most antipsychotic drugs are highly lipophilic, highly membrane- or protein-bound, and accumulate in the brain, lung, and other tissues with a rich blood supply. – They also enter the fetal circulation and breast milk. It is virtually impossible and usually not necessary to remove these agents by dialysis. – Volume of distribution is large 20 L/kg and metabolized in liver by CYP2D6; elimination t1/2 is variable (18-30 hr). – Tolerance to the sedative and hypotensive action develops within day or week.

SECOND -GENERATION ANTIPSYCHOTIC AGENTS or ATYPICAL ANTIPSYCHOTICS

Second generation antipsychotics have weak D2 blocking but potent 5-HT2 antagonistic activity. Extrapyramidal side effects are minimal, and they may improve the impaired cognitive function in psychotics.

CLOZAPINE • First atypical antipsychotic agent; Week D2 blocking action; few/no extrapyramidal effects • Both –ve and +ve symptoms of schizophrenia are improved; used as a reserve drug in resistant schizophrenia. • The differing pharmacological profile may be due to its relative selectivity for D4 receptors (which are sparse in basal ganglia) and additional 5-HT2 as well as a blockade. • Clozapine is metabolized primarily by CYP3A4 with an average t1/2 of 12 hours. Its major limitation is higher incidence of agranulocytosis (0.8%) and other blood dyscrasias; weekly monitoring of leucocyte count is required. High dose can induce seizures even in nonepileptics. Other side effects are sedation, unstable BP, tachycardia, urinary incontinence, weight gain and precipitation of diabetes. Agranulocytosis is a rare condition that occurs when the bone marrow does not make enough neutrophils

Risperidone • Combination of D2 + 5-HT2 receptor blockade. • In addition it has high affinity for α1, α2 and H1 receptors; blockade of these may contribute to efficacy as well as side effects like postural hypotension. • Risperidone is more potent D2 blocker than clozapine; extrapyramidal side effects are less only at low doses (<6 mg/ day). Prolactin levels rise during risperidone therapy, but it is less epileptogenic than clozapine. • Caution: increased risk of stroke in the elderly.

Olanzapine (broader spectrum of efficacy covering schizo-affective disorders) • resembles clozapine in blocking multiple monoaminergic (D2, 5- HT2, α1, α2) as well as muscarinic and H1 receptors. Both positive and negative symptoms of schizophrenia appear to be benefited. • A broader spectrum of efficacy covering schizo-affective disorders, and it is approved for use in mania. Monotherapy with olanzapine may be as effective as a combination of lithium/valproate + benzodiazepines. • Weaker D2 blockade results in few extrapyramidal side effects and little rise in prolactin levels. • Incidence of stroke may be increased in the elderly. • Agranulocytosis has not been reported with olanzapine. • Olanzapine is metabolized by CYP1A2 and glucuronyl transferase. The t1/2 is 24-30 hours.

Quetiapine • This new short-acting (t1/2 is 6 hours) atypical antipsychotic requires twice daily dosing. • It blocks 5-HT1A, 5-HT2, D2, α1, α2 and H1 receptors in the brain, but D2 blocking activity is low: extrapyramidal and hyperprolactinaemic side effects are minimal. • ADR: – quite sedating, postural hypotension, urinary retention – Weight gain and rise in blood sugar are infrequent • Use: benefit negative symptoms of schizophrenia, but can be used in mania /bipolar disorder. • It is metabolized mainly by CYP3A4; can interact with macrolides, antifungals, anticonvulsants, etc.

Atypical antipsychotic agent	Distinctive features
Aripiprazole	• partial agonist at D2 and 5-HT1A receptor • It is minimally sedating, may even cause insomnia • Metabolized by CYP2D6 and CYP3A4. • ADR: nausea, dyspepsia, constipation and light-headedness. hyperprolactinaemia, hypotension and Q-T prolongation are not frequent.
Ziprasidone	• D2 + 5-HT2A/2C + H1 + α1 receptor blocking activity. • Efficacy in schizophrenia has been related equivalent to haloperidol
Amisulpiride	• Congener of sulpiride (typical antipsychotic) • High affinity to D2 (and D3) receptor and has low affinity for 5- HT2 receptor. • Not sedative.
Zotepine	• D1+D2 and 5-HT2, α1 receptor blocking activity. • It also inhibits NA reuptake. • Both positive and negative symptoms of schizophrenia appear to be benefited. • It has lower seizure threshold. • ADR: Weight gain, hyperglycemia.

ADVERSE EVENTS

• CNS: Drowsiness, lethargy, mental confusion, weight gain (not with haloperidol), aggravation of seizures in epileptics. • CVS: Postural hypotension, palpitation, inhibition of ejaculation (especially with thioridazine) are due to a adrenergic blockade; Q- T prolongation and cardiac arrhythmias are risk of overdose with thioridazine, pimozide and ziprasidone. • Anticholinergic Dry mouth, blurring of vision, constipation, urinary hesitancy in elderly males. • Endocrine Hyperprolactinemia (due to D2 blockade) is common with typical neuroleptics and risperidone. This can lower GH levels, but amenorrhoea, infertility, galactorrhoea and gynaecomastia occur infrequently after prolonged treatment. • Metabolic effect: Elevation of blood sugar and triglyceride.

• Extrapyramidal disturbances: Dose-limiting side effects. – The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. – Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment. • Hypersensitivity reaction: Chlestatic jaundice, myocarditis, agranulocytosis. • Miscellaneous: Weight gain often occurs with long term antipsychotic therapy; blood sugar and lipids may tend to rise. Risk of worsening of diabetes and blue pigmentation of exposed skin, and retinal degeneration. Tardive dyskinesia is a disorder that involves involuntary movements, especially of the lower face (tongue, lips, face, trunk, and extremities).

Therapeutic uses

• Treatment of schizophrenia • Prevention of severe nausea and vomiting • Other uses: – Treatment of mania, organic brain syndromes, anxiety. – Chlorpromazine is used to treat intractable hiccups. – Risperidone and haloperidol are also commonly prescribed for this tic disorder. Also, risperidone and aripiprazole are now approved for the management of the disruptive behavior and irritability secondary to autism (is a disorder of neural development characterized by impaired social interaction).

Lecture Note		
Subject: Ph.Cology, 404T	**SEM-4th**	**UNIT-II**
Submitted By:	**Prasenjit Mishra**	**HCP-345-BBSR**

CLINICAL EVALUATION OF NEW DRUGS

Introduction

• Clinical trial is a systematic investigation in human subjects for evaluating the safety & efficacy of any new drug.

• Clinical trials are a set of tests in medical research and drug development that generate safety and efficacy data for health interventions in human beings.

Clinical trials are conducted only when

- ✓ satisfactory information has been gathered on the quality of the nonclinical safety
- ✓ Health authority/ethics committee approval is granted in the country where approval of the drug is sought.
- ✓ Clinical Trial is the mainstay for bringing out New Drugs to the Market.

Drug Review Steps

- ✓ Preclinical (animal) testing.
- ✓ An investigational new drug application (IND): outlines what the sponsor of a new drug proposes for human testing in clinical trials.
- Phase 1 studies
- Phase 2 studies
- Phase 3 studies
- ✓ Submission of New Drug Application (NDA) is the formal step asking the FDA to consider a drug for marketing approval.
- ✓ FDA reviewers will approve the application or find it either "approvable" or "not approvable."
- ✓ Phase 4 studies

Drug review

• Before one can initiate testing in human beings, extensive pre- clinical or laboratory research is required

• Research usually involves years of experiments in animal and human cells.

• If this stage of testing is successful, the sponsor then provides this data to the FDA requesting approval to begin testing in humans.This is called an Investigational New Drug (IND) Application

• If approved by the FDA, testing in humans begins. This is done through a formally written and approved protocol.

After completion of Preclinical evaluation phase

Prephase I Activities

- ✓ Preclinical Data Review: Drug Discovery Team - Efficacy - Safety Pharmacology - Toxicology ADME.
- ✓ Preparation of Investigator's Brochure - Summaries of Preclinial data with clinical Extrapolation. Prediction of Clinical Effects & Safety.
- ✓ Filing of Investigational New Drug Application with DCGI.

IND (Investigational New Drug) Application Filing

A) Once preclinical studies have indicated the safety and efficacy of a drug an IND application has to be filed with the regulatory authorities

B) For obtaining regulatory Approval for Phase I, Phase II and Phase III clinical evaluation.

C) Contents of IND application

- Preclinical Data (All data from animal studies)
- Information on composition and source of drug
- Chemical and manufacturing information
- Proposed clinical plans and protocol
- Ethical Committee Clearance

D) Clinical Evaluation needs Prior Regulatory and IRB (Institutional Review Board) Clearance.

E) Phase-wise clearances have to be obtained.

F) The End Result of Phase I-III studies is the filing of NDA (New Drug Application) for obtaining Marketing Permission from DCGI.

Phase 0 study / Microdosing

- Study of new drug in microdoses to derive PK information in human before undertaking phase I studies is called PHASE O
- Microdose: Less than 1/100 of the dose of a test substance calculated to produce pharmacological effect with a max dose ≤100 micrograms
- Objective: To obtain preliminary Pharmacokinetic data.
- Preclinical Data: Subacute toxicity study in one species by two routes of administration.
- These are very early studies of the pharmacodynamic and pharmacokinetic properties of a potential drug in humans.
- Microdosing approach could 'accelerate' drug development without compromising clinical safety
- Microdosing helps researchers select better drug candidates for clinical trials by providing early human PK and bioavailability data.

Advantages:

Less chances of adverse effects, Short duration, Less no. of volunteers, Reduced cost of development, Reduced drug development time

Limitations: Study mainly based on PK parameters - not efficacy and safety based, Agents having different kinetic characteristics between microdose and full dose are not evaluated by phase 0 trials, Of Limited use for agents having Non linear PKs , The laboratory parameters are very limited and expensive, researchers have to depend on BA/BE labs

Phase I Study/ Clinical trial

Basic pre-requisites • Preclinical data • IND application • Approval by the regulatory authority • Protocol approval by the Ethics Committee • Informed consent • Adherence to ***Declaration of Helsinki /ICH*** ***(International Council for Harmonization)-GCP (Good Clinical Practice guidelines***, at the start as well as from time to time, during the study.

Kinds of Phase I • SAD: single ascending dose studies • MAD: multiple ascending dose studies • Food Effect: investigates differences in absorption caused by food.

Single ascending dose studies (SAD) • Small groups (3) of subjects are given a single dose of the drug while they are observed and tested for a period of time. • If no adverse effects ☾ dose is escalated with 3 new healthy subjects • If toxicity is observed then ☾ 3 more subjects are given the same dose and • if found toxic ☾ the dose is considered as max. tolerated dose (MTD).

Multiple ascending dose studies (MAD) • conducted to understand the pharmacokinetics and pharmacodynamics of multiple doses of the drug. • A group of patients receives multiple low doses of the drug • Samples (of blood, and other fluids) are collected at various time points • Analyzed: How the drug is processed within the body.

• First stage of testing in human subjects

• Designed to assess the safety, tolerability, PK and PD of drug.

• 20-25 healthy volunteers

• Patients: Subject

• Duration: 6-12 months

• No blinding / Open labelled

• Healthy human volunteers: Most commonly used. (Non-Therapeutic Research) - Subjects receive no therapeutic benefit by participation - Ethical issue. • Patient Volunteers: Cytotoxic drugs, AIDS therapy - Patients in advanced stage of disease

Reasons for Using Healthy Volunteers • Large numbers available (vs. Patients) • Rapid recruitment rate • Potential risks are considerably reduced • Results not confounded by presence of disease variables • More homogenous group • Greater compliance with Protocol • In case of ADR's Chances of Speedy and Complete recovery are better • Advantages > Disadvantages

Patient Volunteers F Whenever Preclinical Toxicity Data indicates potential risks for subjects & Ethical Concerns preclude use of healthy human subjects e.g. Cancer/AIDs/Psychiatric patients • Dose range of interest is appropriate to determine in patients than in healthy volunteers

Special Population Healthy Volunteers It is now a regulatory requirement to include • Women of child bearing age • Children, if NCE is proposed to be used in them. • Elderly (>65 years) of age.

Limitations of Phase I • Trial restricted to homogenous subjects • Performance extrapolated to heterogeneous market place

Phase II Study/ Clinical trial

Phase II Study/ Clinical trial

• Phase II Types: • Phase IIA: Designed to assess dosing requirements

• Phases IIB: Designed to study efficacy

• Therapeutic Exploratory Trial

• 20-300 Subjects

• To confirm effectiveness, monitor side effects, & further evaluate safety

• First in patients (who have the disease that the drug is expected to treat)

• Duration: 6 months to several years.

Objectives • Efficacy in patients (primary objective) • Safety issues (secondary objective) • Optimum dose finding • Dose efficacy relationship • Therapeutic dose regimen • Duration of therapy • Frequency of administration • Therapeutic window

Pre-requisites • Review of Phase I data • Innovator/ Experts • IRB • DCGI • Prior approval by IRB and DCGI is Mandatory

* For New Actions of a marketed drug, start with Phase II (Phase I exemption obtained)

Phase II Study/ Clinical trial • Phase II Types: • Phase IIA: Designed to assess dosing requirements • Phases IIB: Designed to study efficacy

Phase III Study/ Clinical trial

• Therapeutic confirmatory trials.

• Large scale, multicentre, Randomised, Controlled trials.

• Target population: several 100’s to 3000 patients.

• Takes a long time: up to 5 years

• To establish efficacy of the drug against existing therapy in larger number of patients, method of usage, & to collect safety data etc.

Objectives • To assess overall and relative therapeutic value of the new drug Efficacy, Safety and Special Properties

• To determine optimal dosage schedule for use in general

• The dosage schedule in C.T.'s should be as close as possible to its anticipated clinical use

Prerequisites • Efficacy and dose schedule defined in Phase II studies

• No gross ADR's

• Long term preclinical safety studies completed

- Chronic Toxicity
- Reproductive toxicity
- Carcinogenicity

• Marketing inputs favourable

• IRB and DCGI approval obtained

Subtypes

• Phase IIIA: to get sufficient and significant data.

• Phase IIIB: allows patients to continue the treatment, Label expansion, additional safety data.

• Phase III B studies are known as "label expansion" to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing

Phase IIIa • Prior to NDA

• Generates data on safety and efficacy

• Phase IIIb

• After the NDA but prior to the approval and launch.

• These may supplement or complete the earlier trials or may be directed to Phase IV trials. Phase III

Phase III Studies : End of Clinical Trial Activities

Sponsor: Expert Committee review of Efficacy, safety and potential sales (Profit).

• ***Go-No Go decision*** to file new drug application with DCGI

• ***Expert review by DCGI's Committee***

• DCGI approval

• **NCE (new chemical entity)** marketed - Phase IV begins

NDA: New Drug Application /NDA Refers to New Drug Application

• Formal proposal for the FDA/DCGI to approve a new drug for sale

• Sufficient evidences provided to FDA/DCGI to establish:

• Drug is safe and effective.

• Benefits outweigh the risks.

• Proposed labeling is appropriate.

• NDA contains all of the information gathered during preclinical to phase III

• NDA can be thousands of pages long • Can take 2-3 years for FDA to review

Phase IV Study/ Clinical trial

Objectives

• Confirm the efficacy and safety profile in large populations during practice

• Detect the unknown/rare adverse drug reaction/s

• Evaluation of over-dosage

• Identifications of new indications

• Dose refinement: Evaluation of new formulations, dosages, durations of treatment

• Evaluation in different age groups / types of patients

• Comparative Benefit-Risk assessment

• Benefit-Cost assessment (Pharmaco- economics)

• Drug usage in the community • Quality Of Life assessment

• Done after drug has been marketed

• Post Marketing Surveillance (PMS).

• No fixed duration / patient population

• Studies continue to collect data about effects in various populations & side effects from long term use.

• ***These are primarily observational or non- experimental in nature.***

• Helps to detect rare ADRs, Drug interactions

• Also to explore new uses for drugs [***Sometimes called Phase V]***

PERIODIC SAFETY UPDATE REPORTS (PSUR)

• To be submitted by the manufacturer every 6 months for 2 yrs and then annually for next 2 yrs after marketing approval

Phase IV Study / Clinical trial

• Harmful effects discovered may result in a drug being no longer sold, or restricted to certain uses.

EXAMPLE:- On September 30, 2004, Merck withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use.

REPORTING of ADR

• If Health care personal suspects that a particular medication is associated with an adverse event observed during the course of caring for a patient, he can report the ADR to a formal reporting system.

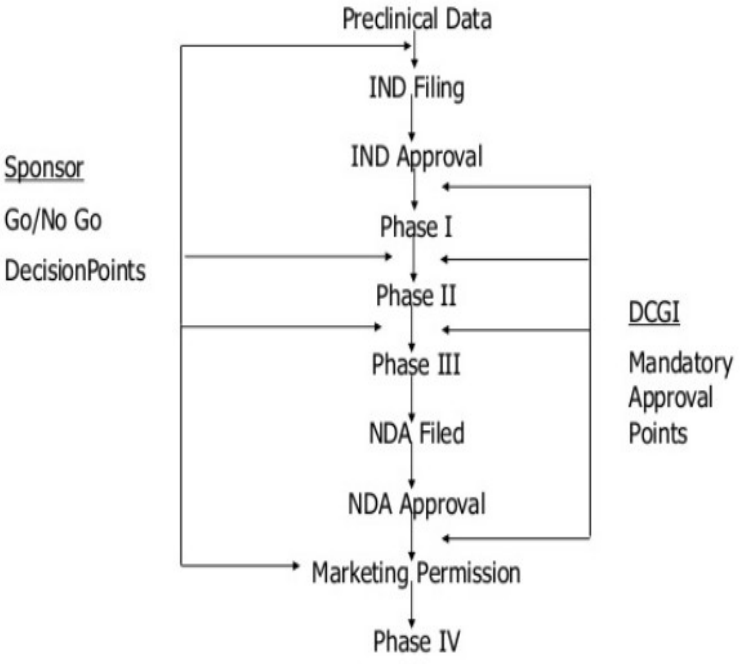
Various reporting systems are:

WHO International System USFDA –Medwatch

UK –Yellow card system

INDIA – National Pharmacovigilance Programme (CDSCO)

Clinical Drug Development Phase



Phases of clinical trial

- Exploratory CT's (Proof of Concept): Phase 0, Phase I, Phase II
- Definitive CT's (Pivotal): Phase III, Phase IV

Phase 0 / Phase I / Phase II / Phase III: Developmental CT's (Premarketing Phase of Clinical Drug Development)

Phase IV: Post marketing Phase

PHASE II CLINICAL TRIALS:

- **Phase IIa**
- EARLY PHASE
- Pilot clinical trials
- 20-200 PATIENTS
- Not multicentric
- SINGLE BLIND comparison with a standard drug

- **Phase IIb**
- LATE PHASE
- Pivotal clinical trials
- 50-300 PATIENTS
- Multicentric
- DOUBLE BLIND compared with a placebo or standard drug

Phase III

- **Phase IIIa**
- Prior to NDA
- Generates data on safety and efficacy

- **Phase IIIb**
- After the NDA but prior to the approval and launch.
- These may supplement or complete the earlier trials or may be directed to Phase IV trials.

Lecture Note		
Subject: Ph.Cology, 404T	**SEM-4th**	**UNIT-II**
Submitted By:	**Prasenjit Mishra**	**HCP-345-BBSR**

Factors Modifying Action of Drugs

Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions will occur.

FACTORS were:-

1. **Physiological Factors.**
2. **Pathological Factors (Diseases)**
3. **Genetic Factors**
4. **Environmental Factors**
5. **Interaction with other drugs**

1. Physiological Factors

a. Age

The adult dose is for people between 18 and 60 years of age. The tissues of an infant & child are highly sensitive to large number of drugs. Children under 12 yrs require fraction of adult dose because:

1. Drug metabolizing enzyme system is inefficient in them (Glucuronidation takes 3 months to develop)

2. Their barriers are not fully developed (BBB, blood aqueous barrier), thus are more sensitive to CNS stimulants. All parts of the body are affected by the drug.
3. Infants have an immature renal tubular transport system. Penicillin, streptomycin and amino glycosides are not administered. After one year of age, elimination by kidneys is increased.
4. Hepatic metabolizing capacity is also under developed. *Chloramphenicol may cause grey baby syndrome.*

The dose for a child is calculated from the adult dose up to 8 yrs of age. The average adult dose is for an individual of medium built. For very thin or obese individual the dose may be modified using either the body surface area or ***body weight***. i.e.

Surface area is found from height and weight, and is around 1.7-1.8/m^2. , 1.7 (average body surface area in AD).

$$\text{Dose to be prescribed} = \frac{\text{Body surface area } (m^2) \times \text{adult dose}}{1.7}$$

$$\text{Dose to be prescribed} = \frac{\text{Wt in kg} \times \text{adult dose}}{70}$$

$$\text{Child dose} = \frac{\text{Body surface area in m2 of child} \times \text{adult dose}}{}$$

$$\text{Child dose} = \frac{\text{Age} \times \text{adult dose}}{\text{Age} + 12} \quad \text{(young's formula)}$$

$$\text{Child dose} = \frac{\text{Age} \times \text{adult dose}}{} \quad \text{(Dilling's formula)}$$

Body weight

Dose is given per kg body weight. Average muscular weight is between 50 and 100 kg, with 70 kg being the average.

Newborns

The drug dosage of newborn is decreased because:

a. gastric acid secretion are not adequate e.g.

GIT absorption of ampicillin and amoxicillin is greater in neonates due to decreased gastric acidity

b. liver microsomal enzymes (glucuronyl transferase) are deficient

Administration of Chloramphenicol may lead to Grey baby syndrome because of inadequate glucouronidation of chloramphenicol resulting in drug accumulation

c. Plasma protein binding is less

d. GFR & tubular secretions are not adequate.

e. There is immaturity of blood brain barriers in neonates.

Sulfonamides may lead to hyperbilirubinemia and kernicterus

Children

In children Tetracyclines may cause permanent teeth staining

Corticosteroids may lead to growth & development retardation

Antihistaminics may cause hyperactivity.

Geriatric age group (> 60 yrs)

Patient requires special consideration because physiological changes occur with age are to be kept in mind such as:

1. Reduced body weight
2. Reduced body fat
3. Reduced intestinal motility & mesenteric blood flow.
4. Reduced renal & hepatic functions
5. Altered mental functions

Elderly often require lesser doses than adults because they are prone to suffer from adverse drug reactions. If liquid preparations are available, they should be preferred as are convenient for absorption.

Liver functions are impaired. Drugs like diazepam, theophylline having lower therapeutic index, may have much larger half lives (2 hrs in normal 90 hrs in old)

Kidney functions are also impaired. Drugs like Digoxin, lithium and amino glycosides have decreased excretion

Plasma protein binding is decreased leading to greater amounts of active drugs.

Increased sensitivity to CNS depressants like diazepam, morphine also occurs

b. Sex

Evidences show that men and women may respond differently to same drugs. This may be due to body size, and amount of body fats. But there are also some less easily explained differences in gender –specific drug response, Aspirin shows greater benefit in men than women in cardiovascular diseases
There appears to be difference in the activity of liver enzymes b/w men and women
Since the activity of enzymes vary that can result in major difference in drug response

This difference in liver activity may explain why women routinely wake up from general anesthesia several minutes before a man given an equal dose.

Testosterone increases the rate of biotransformation of drugs.Decreased metabolism of some drugs in female (Diazepam) occurs. Females are more susceptible to autonomic drugs (estrogen inhibits choline esterase). Drugs used for ulcer may cause increased prolactin.

During menstruation, salicylates and strong purgatives should be avoided as they may increase bleeding.

c. Pregnancy

In pregnancy following are to be considered: Causes several physiological changes that influence drug disposition.

1. Cardiac output
2. GFR and renal elimination of drugs.
3. Volume of distribution
4. Metabolic rate of some drugs

Volume of drug distribution is increased(total body water may increase by up to 8 liters) providing large space for water soluble drugs.

Maternal plasma albumin concentration is reduced,more free drugs will be available. Metabolic rate is increased, so the free drugs will be available for elimination.

Cardiac out put is increased, leading to increased renal blood flow and glomerular filtration and increased renal elimination of drugs.

Lipophilic drugs cross placental barrier & are slowly excreted.

During pregnancy, uterine stimulants, strong purgatives and drugs likely to have teratogenic effects should be avoided, especially during first trimester no drug should be given unless absolutely necessary.

During labour, morphine should be avoided as it crosses placental barrier and depresses respiration in newborn.

d. Plasma Protein Binding

Malnutrition causes decreased amino acids, decreased proteins leading to decreased binding sites for drugs.

e. Body weight

Dose is given per kg body weight. Average muscular weight is between 50 and 100 kg, with 70 kg being the average.

f. Lactation

During lactation, drugs may be excreted through milk and may affect the infant e.g. some purgatives, penicillin, chloramphenicol and oral anticoagulants.

g. Food

Drugs are better absorbed in empty stomach. To prevent gastric irritation most drugs are taken after or between foods, which affects the outcomes. Antimotion drugs are taken on empty stomach. Helminthes (for evacuation of worms) are also taken on empty stomach.

h. Allergy

Allergy is the abnormal response of drug resulting from antigen-antibody reaction, leading to liberation of histamine and histamine-like substances; therefore, there may be skin rashes, urticaria, bronchoconstriction and fall of blood pressure. Allergic reactions may occur immediately or may be delayed for many days.

Immediate and acute allergic reactions lead to acute anaphylactic shock which is dangerous for patient and may even be fatal e.g. penicillin, sera, vaccines. Steps which can be taken include:

1. History taking of previous allergic reactions
2. Test dose should be given first
3. Drugs required to deal with emergency should be kept ready

Sometimes skin rashes or urticaria along with fever and pain in joints and swelling of lymph nodes may occur after a few days. This is delayed type of allergy called serum sickness type reaction.

i. Drug Dependence (Drug addiction)

Drug dependence is a state of periodic or chronic intoxication which is detrimental to person and society. It becomes almost impossible to carry out normal physical functions without the drug.

Components of phenomenon of addiction include:

1. Euphoria- sense of happiness and forgetfulness
2. Tolerance- due to increased production of enzymes
3. Psychic dependence (Habituation)- person desires but in absence of drug no harm occurs
4. Physical dependence-
5. Withdrawal symptoms (Abstinence syndrome)- symptoms opposite pharmacological actions of drug develop in absence of drug

2. Pathological Factors

Diseases cause individual variation in drug response

(A) Liver Disease

In liver diseases, prolong duration of action occurs because of increased half life. Plasma protein binding for warfarin, tolbutamide is decreased leading to adverse effects

If hepatic blood flow is reduced, clearance of morphine- propanolol may be affected.

Impaired liver microsomal enzymes may lead to toxic levels of Diazepam, rifampicin and theophylline

(B) Renal Disease

GFR, tabular function and plasma albumin may be affected leading to abnormal effects of digoxin, lithium, gentamycin and penicillin

(C) Malnutrition

Plasma protein binding of drugs is reduced along with the amount of microsomal enzymes, leading to increased portion of free, unbound drug e.g. Warfarin

3. Genetic Factors

Genetic abnormalities influence the dose of a drug and response to drugs. It affects the drug response in individuals at 2 levels.

1. At the level of receptors

2. At the level of drugs metabolizing enzyme

Thus, interfering with the functions such as rate of plasma drug clearance.

Pharmacogenetics is the study of the relationship between genetic factors and drug response.

Idiosyncrasy

Idiosyncrasy is the abnormal drug reaction due to genetic disorder. It is the unpredictable response seen on first dose of drug on hereditary basis. This may be due to

1. Acetylation.

2. Oxidation
3. Succinylcholine apnea
4. Glucose 6-phosphate dehydrogenase deficiency.

All individuals do not respond in similar way to same drug. Idiosyncrasy is used to describe abnormal drug response on administration of first dose.

Genetic Polymorphism

The existence in a population of two or more phenotypes with respect to the effect of a drug. E.g. Acetylation enzymes deficiency

Acetyl transferase (non-microsomal) affects Isoniazid, sulphonamides, etc.

Slow acetylator phenotype may show peripheral neuropathy .

Rapid acetylator phenotype may show hepatitis

Pseudocholinesterase deficiency

Succinyl choline is a skeletal muscle relaxant. Succinylcholine apnea may occur due to paralysis of respiratory muscles.

Malignant hyperthermia

Occurs by succinyl choline due to inherited inability to chelate calcium by sarcoplasmic reticulum resulting in Ca release, muscle spasm and rise in temperature.

Oxidation Polymorphism

In case of Debrisoquine

1. Extensive metabolizers (EM) need larger dose.

2. Poor metabolizers (PM) – need smaller dose.

Deficiency of Glucose-6 phosphate dehydrogenase (G-6-PD)

G-6-PD Deficiency in RBCs leads to haemolytic anaemia upon exposure to some oxidizing agents like

1. Antimalarial drug, primaquine

2. Long acting sulphonamides
3. Fava beans (favism).

4. Environmental Factors

a. Route of Administration

Some drugs are incompletely absorbed after oral intake, when given intravenously; their dose has to be reduced. Examples include morphine and magnesium sulphate. Magnesium sulphate when given orally is osmotic purgative, but its 20% solution is injected intravenously to control the convulsions in eclampsia of pregnancy.

b. Time of Administration

Hypnotics (producing sleep) act better when administered at night and smaller doses are required. Amonoglycosides like streptomycin when given intravenously cause neuromuscular blockage, which is not observed after intramuscular injection.

c. Effect of Climate

Metabolism is low in hot and humid climate. Purgatives act better in summer while diuretics act better in winters. Oxidation of drugs is low at higher altitudes.

d. Racial Differences

Castor oil, a purgative, is ineffective in Chinese. The dilating effect of ephedrine in fair people on pupil is absent in Negroes.

e. Preparation of Drug

Drugs in solid forms disintegrate slowly. Onset of action is rapid when drug is given in liquid form.

f. Age of Drug

Action may be modified if kept for longer durations. Outdated tetracyclines give rise to excretion of amino acids in urine. Chloroform and carbon tetrachloride become toxic if kept for long durations.

g. Acidic or Basic Medium

If GIT has decreased acidity, acidic drugs like benzyl penicillin are not effective orally.

h. Effect of Disease

Certain drugs are only effective in disease conditions. These include antipyretics like aspirin and paracetamol, which do not reduce temperature in case of healthy individuals.

Iron is better absorbed in iron deficiency anemia. As the anemia improves, it has less response.

Hyper susceptibility to Drugs

Variations in individuals leading to prolonged effects of drugs. Examples include diazepam, 2 mg of which are used as antianxiety producing no hang overs. In hyper susceptible individuals, the drug has prolonged action causing hangovers and hypnotic actions.

Opioids like morphine cause analgesia and sedation in 10 mg dose effective for 4-6 hours. In hyper susceptible individuals, effect might be prolonged to 10-12 hours. These are individual based variations.

Hypersensitivity

Hypersensitivity is the quantitatively abnormal response with certain groups of drugs. Response is seen in sub therapeutic doses not capable of producing pharmacological actions. This has immunological basis, e.g. allergy. 25% of the drugs show hypersensitivity.

Hematological disorders can occur more pronounced in atopic individuals, who are already exposed to antigens, e.g. ashthemics are more prone to allergic reactions.

Nearly all drugs show hypersensitivity in some category, which might be self limiting or even life threatening. Penicillin when administered may cause anaphylactic shock. High molecular weight drugs have a greater tendency to show hypersensitivity. History taking

is helpful in predicting hypersensitivity. Test dose can be given intradermally and localized reactions can be seen.

Tolerance

Resistance to normal therapeutic dose of drug, producing lesser response to normal therapeutic dose is known as tolerance. This is acquired character. Examples include morphine, person is initially responsive, if continued, changes occur at cellular and pharmacokinetic level, reducing the action. Thus one has to increase the dose of drug to overcome.

Alcoholics do not respond to hypnotics and analgesics, dose of which has to be increased many folds. In fact they may even tolerate toxic levels.

Cross Tolerance

A person tolerant to drugs resembling in chemical structure is known as cross tolerance. Those drugs resembling in chemical structures show cross tolerance. If a person is tolerant to morphine, he also shows tolerance to pathedine (synthetic derivative) and codeine.

Complete cross tolerance is observed in cases like diazepam and flurezepam

Incomplete cross tolerance occurs with the drugs sharing the same pharmacological properties. Examples include barbiturates and general anesthetics, site of action is CNS, incomplete cross tolerance may be observed although they are not resembling chemically, but having same pharmacological properties.

Tachyphylaxis

Repeated administration of a drug at short intervals of time leads to a rapidly developing tolerance. This occurs with indirectly acting drugs. On repeated administration, depletion of endogenous receptors occurs. It is also known as acute tolerance. Example includes ephedrine, which acts by releasing noradrenalin from adrenergic stores. After repeated administration, these stores are exhausted and pharmacological action is not restored even on increasing the dose.

5. Interactions of Drugs

a. Synergism

Synergism is the facilitation/potentiation of pharmacological response by concomitant use of two drugs.

I. Potentiation

The total effect will be more than the sum of their individual effects. Examples are:

1. Acetylcholine + physostigmine. Physostigmine inhibits the action of esterase prolonging the effect of acetylcholine.
2. Levodopa (Parkinsonism) + carbidopa/benserazide. Levo dopa is decarboxylated peripherally, carbidopa inhibits the decarboxylase.
3. Sulfonamide (effective against some microorganisms) when combined with trimethoprim is effective against a wider range of microorganisms.

The action is more than the normal therapeutic effect.

II. Additive Effect (Summation)

In this case the total pharmacological action of two drugs will be equal to the sum of their individual effect on simultaneous administration. The response is not more than their total algebraic sum. e.g.

1. Aspirin + paracetamol as analgesic/ antipyretic
2. Ephedrine + theophylline as bronchodilator
3. Nitrous oxide + ether as general anesthetic
4. Antihypertensive drugs
5. Cardiac stimulants

b. Antagonism

When two drugs, administered simultaneously, oppose the action of each other on the same physiological system, the phenomenon is called antagonism. It can be of following types.

1. Chemical antagonism**:**

It involves reduction of the biological activity of a drug by a chemical reaction with another agent e.g. between acids and alkalies: BAL and arsenic. Antacids, used for dyspepsia involve administration of sodium bicarbonate to react with hydrochloric acid. In cases of heavy metal poisoning chelating agents are used like dimerzapam.

In iron poisoning deproxamine is given which binds sulphydral groups forming insoluble complexes which can be easily detoxified.

2. Pharmacological antagonism

Pharmacological antagonism is of two types:

I. Competitive or reversible antagonism**.**

In this type of antagonism the agonist and antagonist compete with each other for the same receptors. The extent of antagonism will depend on the relative number of receptors occupied by the two compounds. Other features are:

a. Antagonist has chemical resemblance with agonist.

b. Antagonism can be overcome by increasing the concentration of the agonist at receptor site. It means the maximal response to agonist is not impaired.

c. Antagonist shifts the dose response curve to right

d. Emax of agonist is obtained with high concentration of agonist

e. Duration of action is short. It depends on drug clearance

Example is of acetyl choline and atropine antagonism on muscarinic receptors. In presence of antagonist, log dose response curve of agonist shifts to right, indicating a higher concentration of agonist is required for same response. Maximum height of the curve can be attained by overcoming the action of antagonist. This leads to a parallel shift of log dose response curve towards right.

II. Non competitive antagonism**:**

Here an antagonist inactivates the receptor in such a way so that the effective complex with agonist cannot be formed irrespective of the concentration of the agonist. This can happen by various ways:

1. The antagonist might combine at the same site in such a way that even higher concentration of the agonist can not displace it.
2. The antagonist might combine at a different site of R in such a way that agonist is unable to initiate characteristic biological response

3. The antagonist might itself induce a certain change in R so that the reactivity of the receptor site where agonist should interact is abolished.

Other features of this antagonism are:

1. Antagonist has no chemical resemblance with agonist.

2. Maximum response is suppressed

3. Although antagonist shifts the dose response curve to right, the slope of the curve is reduced.
4. The extent of antagonism depends on the characteristics of antagonist itself and agonist has no influence upon the degree of antagonism or its reversibility
5. Emax of agonist is decreased even with high concentration of agonist

6. Duration of action is long which depends upon new receptor synthesis.

Example is of phenoxybenzamine and adrenaline at alpha adrenergic receptors.

III. Physiological antagonism:

In this interaction of two drugs, both are agonists, so they act at different receptor sites. They antagonize the action of each other because they produce opposite actions. Classical example of physiological antagonism is adrenalin and histamine. Former causes bronchodilatation while later broncho Constriction. So adrenalin is a life saving drug in anaphylaxis.

Clinical significance of drug antagonism

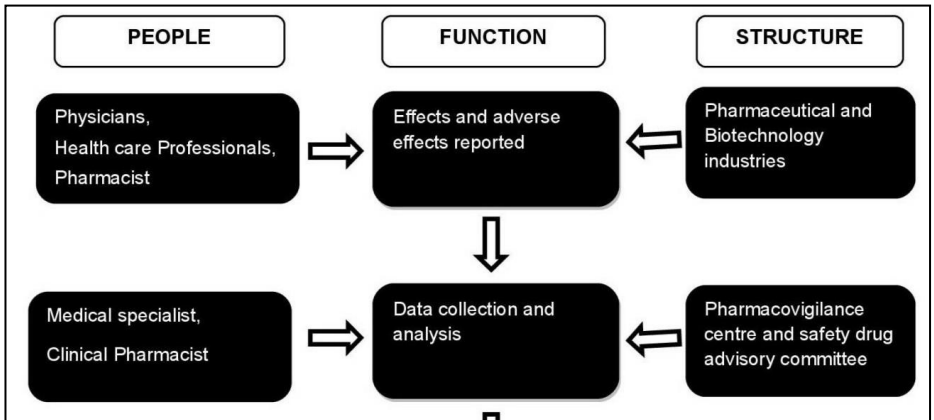
1. It helps to correct adverse effects of a drug e.g. ephedrine and phenobarbitone.
2. It is useful to treat drug poisoning e.g. morphine with naloxone
3. It guides to avoid drug combinations with reduced drug efficacy such a as penicillin and tetracycline combination

Lecture Note		
Subject: Ph.Cology, 404T	**SEM-4th**	**UNIT-II**
Submitted By:	**Prasenjit Mishra**	**HCP-345-BBSR**

ROLE OF PHARMACOVIGILANCE

Scope of PV

The discipline of PV has developed considerably since the 1972 WHO technical report, and it remains a dynamic clinical and scientific discipline. It has been essential to meet the challenges of the increasing range and potency of pharmaceutical and biological medicines including vaccines, which carry with them an inevitable and sometimes unpredictable potential for harm. The risk of harm, however, is less when medicines are used by an informed health profession and by patients who themselves understand and share responsibility for their drugs. When adverse effects and toxicity appear, particularly when previously unknown in association with the medicine, it is essential that they are analyzed and communicated effectively to an audience that has the knowledge to interpret the information. This is the role of PV, of which much has already been achieved. But more is required for the integration of the discipline into clinical practice and public policy. To fulfill the PV obligations for its marketed products as per regulations, a pharmaceutical company in India has to essentially carry out activities such as collection, and expedited reporting of serious unexpected ADRs. A typical setup for PV studies, including people involved on various levels, organizational units and their functions are shown in Figure 1.



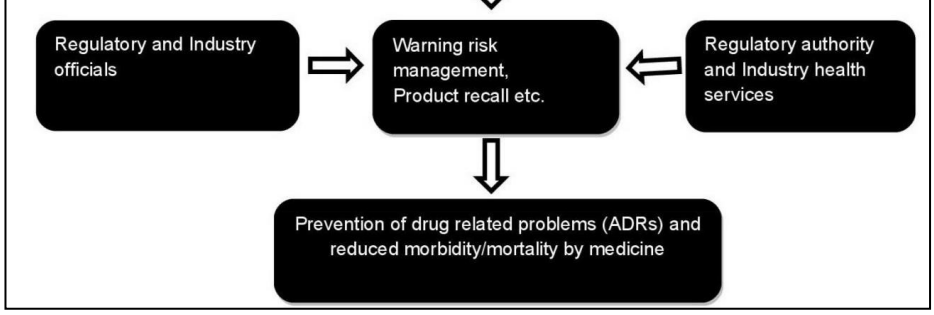
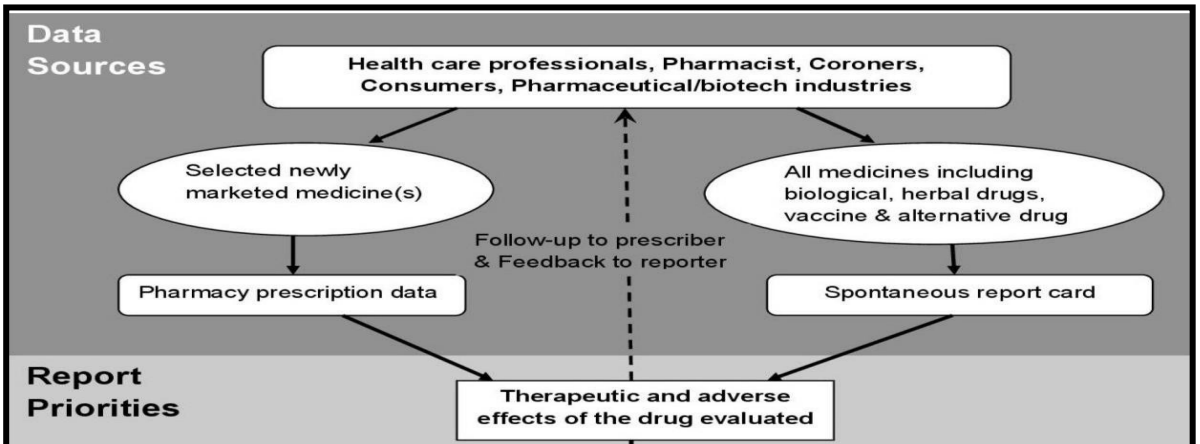
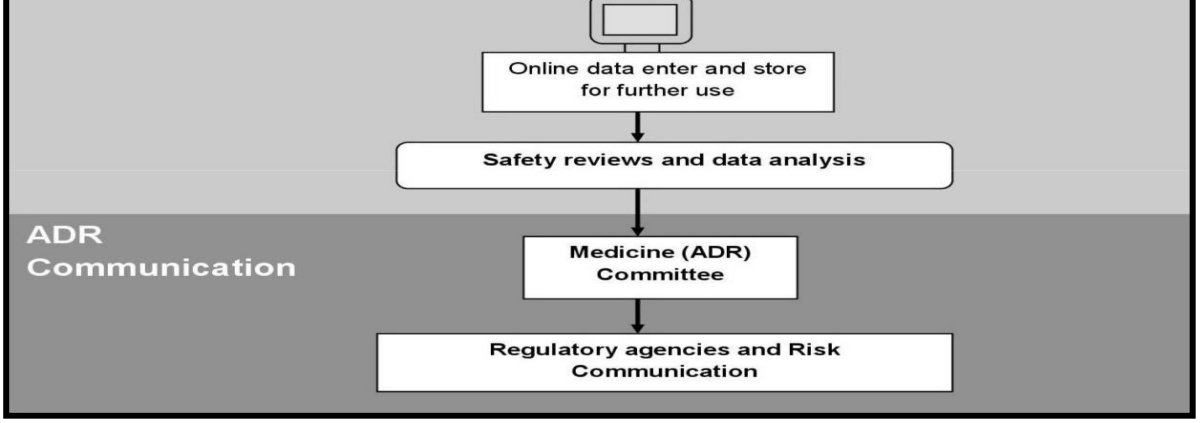


Figure 1. A typical pharmacovigilance setup

PHARMACOVIGILANCE IN INDIA

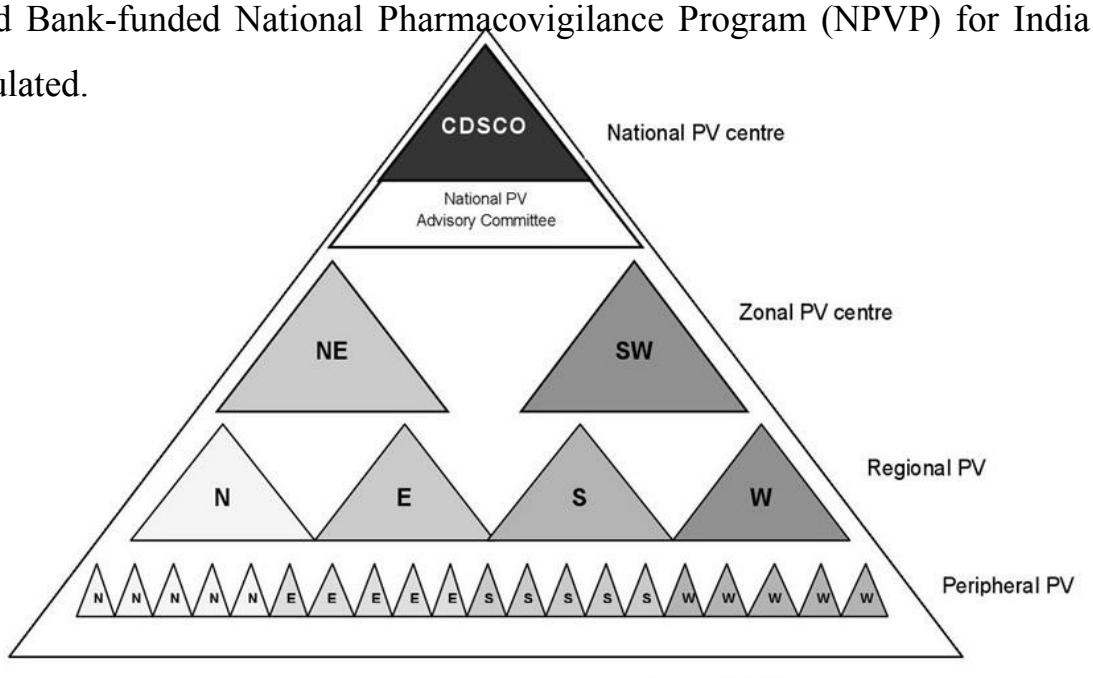
In India, consideration for the surveillance of ADRs developed relatively late, as traditionally there was no concept of surveillance of medicines in the country. Even though PV is still in its infancy, it is not new to India. It was not until 1986 when a few physicians, mainly from academic institutions, called for greater attention to be devoted to the potential adverse effects of prescription medicines and rational prescribing of medicines. This led to the formation of the first ADR monitoring program consisting of 12 regional centers, each covering a population of 50 million, but was unsuccessful. Nothing much happened until a decade later when India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden in 1997. Three centers for ADR monitoring were identified, mainly based in the teaching hospitals:





Pharmacovigilance systematic methods for the Evaluation of Spontaneous Reports collected from different data sources.

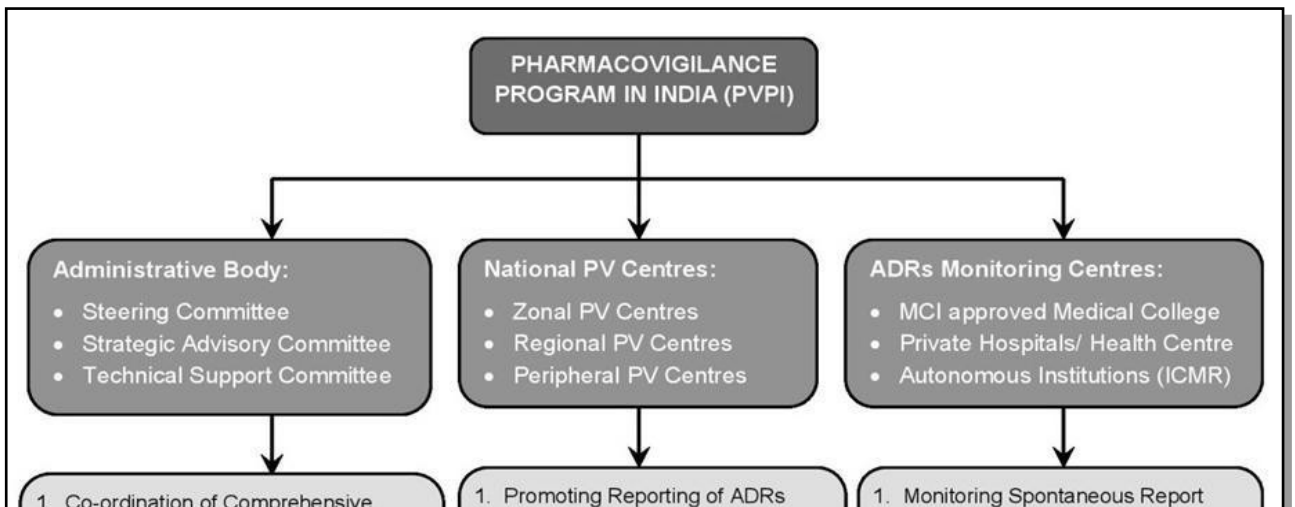
A National Pharmacovigilance Center located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs to medicines marketed in India. However, they were non-functional as information about the need to report ADRs and about the functions of these monitoring centers never reached the prescribers and there was lack of funding from the government. This attempt was unsuccessful, and hence, again from 1 January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program (NPVP) for India was formulated.



National Pharmacovigilance Programme Zones in India

National Pharmacovigilance Program zone structure

The NPVP, established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based at the Central Drugs Standard Control Organization (CDSCO). Two zonal centers, the South-West (SW) zonal center (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East (NE) zonal center (located in the Department of Pharmacology, AIIMS, New Delhi) were to collect the information from all over the country and send it to the committee as well as to the Uppsala Monitoring Centre (UMC) in Sweden. Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center, in turn, would have several peripheral centers (24 in total) reporting to it. The program had three broad objectives. The short-term objective was to foster a reporting culture, the intermediate objective was to involve large number of healthcare professionals in the system in information dissemination, and the long-term objective was for the program to be a benchmark for global drug monitoring.

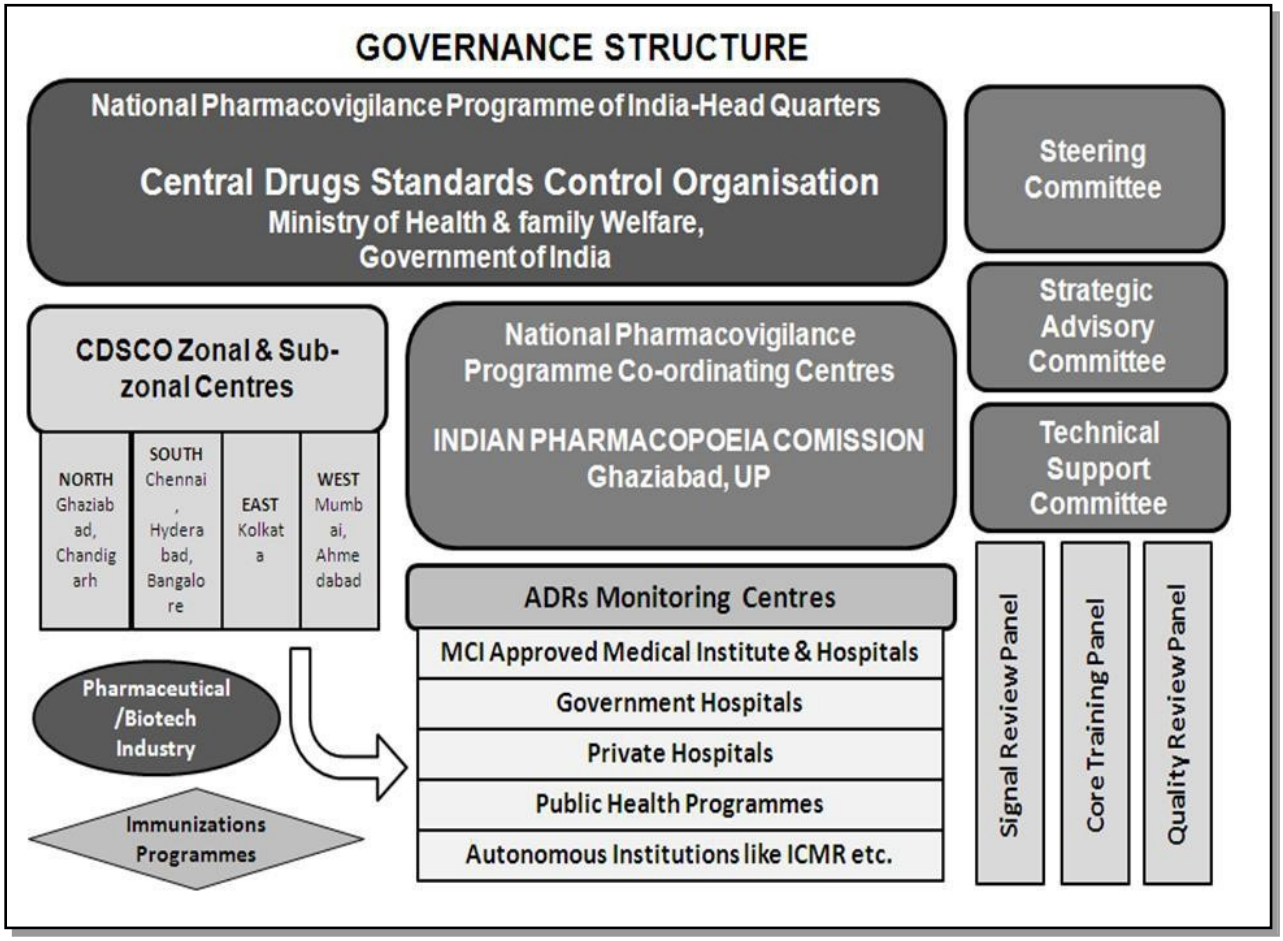


2. Operational Supervision of CDSCO
3. Recommend Procedure & Guidelines for Regulators Interventions

3. Clinically Evaluating Case Reports

3. Post-marketing Surveillance of Medicine

Pharmacovigilance program in India and responsibilities.



Governance structure