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NOVEL DRUG DEVELOPMENT STRATEGIES IN TREATMENT OF PSYCHIATRIC DISORDER

Dr. S. Kusuma Kumari, J. Anjali, B. Jhansi, B.V. Ramana.
Dr K.V. Subba Reddy Institute of Pharmacy, Kurnool.

Abstract:
Psychiatric disorders such as depression, anxiety and schizophrenia are leading causes of disability worldwide, and have a huge societal impact. However, despite the clear need for better therapies, and major advances in the understanding of the molecular basis of these disorders in recent years, efforts to discover and develop new drugs for neuropsychiatric disorders, particularly those that might revolutionize disease treatment, have been relatively unsuccessful. A multidisciplinary approach will be crucial in addressing this problem, and in the first Advances in Neuroscience for Medical Innovation symposium, experts in multiple areas of neuroscience considered key questions in the field, in particular those related to the importance of neuronal plasticity. The discussions were used as a basis to propose steps that can be taken to improve the effectiveness of drug discovery for psychiatric disorders.
Psychiatric disorders are now the most common reason for long-term sickness absence. The associated loss in productivity and the payment of disability benefits places a substantial burden on the economies of many developed countries. The occupational dysfunction associated with psychiatric disorders can also lead to poverty and social isolation. As a result the area of work and psychiatric disorders is a high priority for policymakers.
There are two main agendas: for many researchers and clinicians the focus is on the need to overcome stigma and ensure people with severe psychiatric disorders have meaningful work; however the public health agenda predominantly relates to the more common disorders such as depression and anxiety, which contribute a greater burden of disability benefits and pensions. In this review we attempt to address this second agenda.
Our aim in this review is to highlight the complexity of the area, to stimulate debate and to identify important gaps in knowledge where further research.

Corresponding author:
Dr.S.Kusuma Kumari,
Dr K.V. Subba Reddy Institute Of Pharmacy,
Kurnool.
kusumakumari16@gmail.com
7013872084

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INTRODUCTION:

Definition of Psychotropic Drug:

Psychotropic drug is any drug that has primary effects on behavior, experience, or other psychological functions. Psychotropic or psychoactive Drugs can also be defined as chemicals that affect the brain and nervous system, alter feelings and emotions. These drugs also affect the consciousness in various ways. A broad range of these drugs is used in emotional and mental illness.

General Guidelines Regarding drug administration in psychiatry

- The pharmacist should not administer any drug unless there is a written order. Do not hesitate to consult the doctor. When in doubt in any medication. All medications given must be charted on the patient's case record sheet.

In giving medication:

- ✓ Always address the patient by name and make certain of his identification.
- ✓ Do not leave the patient until the drug is swallowed.
- ✓ Do not permit the patient to go to the bathroom to take medication.
- ✓ Do not allow one patient to carry medicine to another.

Classifications of psychotropic drugs:

- ○ Antipsychotic agents
- ○ Antidepressant agents
- ○ Mood stabilizing agents
- ○ Anxiolytics
- ○ Antiepileptic drugs
- ○ Antiparkinsonian drugs
- ○ Miscellaneous drugs which include the stimulants drugs used in eating disorders, drugs used in deductions drugs used in child psychiatry vitamins calcium channel blockers etc.

ANTIPSYCHOTIC AGENT

- ★ Antipsychotic agents are also known as neuroleptic, major tranquilizers, or phenothiazines.
- ★ This group of drugs has a major clinical use in the treatment of psychosis.
- ★ Psychosis is a state in which a person's ability to recognize reality, to communicate and to relate to others is severely impaired.

Mode of action:

- ➔ Antipsychotic agents are thought to block the dopamine receptors. Dopamine is a chemical which is released in the brain and causes psychotic thinking. Increased production of dopamine transmits the nerve impulses to the brain stem faster than normal. This results in strange thoughts, hallucinations, and bizarre behavior.

CLASSIFICATION: -

Class	Examples of drugs	Trade name	Oral dose mg/day	Parenteral dose (mg)
Phenothiazine	Chlorpromazine	Megatil Largactil Tranchlor	300-1500	50-100 Intramuscular injection only
	Triflupromazine	Siquil	100-400	
	Thioridazine	Thioril, Melleril Ridazin	300-800	30-60 Intramuscular injection only
	Trifluoperazine Fluphenazine decanoate	Espazine Prolinate	15-60 -	1-5 Intramuscular injection 25-50
				Intramuscular injection every 1-3 weeks
Thioxanthenes	Flupenthixol	Fluanxol	3-40	
Diphenyl butyl	Pimozide	Oral	4-20	
Piperidines	Penfluridol	Flumap	20-60 weekly	-
Indolic derivatives	Molindone	Mobam	50-225	-
Dibenzazepine	Loxapine	Loxapac	25-100	-
Atypical antipsychotics	Clozapine Reserpine Olanzapine Quetiapine Ziprasidone	Sizopine, Lozapin Sizodon, Sizomax Oleanz Qutan Zisper	50-450 2-10 10-20 150-750 mg 20-80 mg	
Others	Reserpine	Serpasil	0.5-50	

Indications:

Organic psychiatric disorders:

- Delirium
- Dementia
- Drug induced psychosis and other
- Organic mental disorders

Functional disorders:

- schizophrenia
- schizoaffective disorders
- paranoid disorders
- Mood disorders
- Mania
- Major depression with psychotic symptoms Childhood disorders:
- Attention deficit.
- hyperactivity disorder
- Autism

PHARMACOKINETICS:

- ABSORPTION: Antipsychotics when administered orally are absorbed variably from the gastrointestinal tract, with uneven blood levels.
- DISTRIBUTION: They are highly bound to plasma as well as tissue proteins. Brain

concentration is higher than the plasma concentration.

- ❖ METABOLISM: They are metabolized in the liver and excreted in kidneys.
- ❖ The elimination half-life varies from 10 to 24 hours.

SIDE EFFECTS:

- Extrapyramidal symptoms [EPS].
- Neuroleptic-induced parkinsonism.
- Occur in 40% of patients presenting extrapyramidal symptoms. There are two varieties of parkinsonism symptoms.

A) Akinetic form: It appears in the first week of administration of antipsychotic drugs.

- The characteristics of akinetic form are : The difficulty in masticating movements, weakness, muscle fatigue.

B) Agitating form of parkinsonian symptoms: Tremors at rest, rigidity and mask like face most characteristic feature of parkinsonism are:

- Rigidity of muscles
- Motor retardation
- salivation
- slurred speech
- Mask like face
- shuffling gait

Anticholinergic drugs are given as treatments:

1. Akathisia:

- ➢ Akathisia occurs in 50%of all patients presenting extrapyramidal symptoms:
- ➢ The common characteristics: Restlessness
- ➢ "walking in place ". Difficulty in sitting still, or strong urge to move about referred to as "walkies and Talkies" by haris.
- ➢ Before administering anti parkinsonian medication anxiety should be ruled out.

2.Cardiovascular:

1. Tachycardia
2. Orthostatic
3. hypotension
4. reversible arrhythmias

3.Blood or Hematopoietic:

- ➢ Agranulocytes[decrease in leukocytes system especially with chlorpromazine leukopenia, leukocytosis].

ANTIDEPRESSANTS AGENTS:

- ➔ Antidepressant agents are used in affective disorders or disturbances mainly to treat depressive disorders. caused by emotional or environmental stressors. Several groups of affective disturbances are treatable by antidepressants

Mode of action:

- Serotonin and norepinephrine reuptake inhibitors (SNRIs) block serotonin and norepinephrine reuptake in the synapse, increasing post synaptic receptors stimulation. SNRIs differ in their affinity for the serotonin and norepinephrine transporter.
- Tricyclic antidepressants and Monoamine oxidase inhibitors increase these neurotransmitters, that is norepinephrine and serotonin, to the synaptic receptors in the central nervous system. Tricyclic inhibitors block the reuptake in the central nervous system.

CLASSIFICATION :-

CLASS	EXAMPLES OF DRUGS	TRADE NAME	ORAL DOSE (mg/day)
Tricyclic anti-depressants (TCAs)	Imipramine Amitriptyline Clomipramine Dothiepin Mianserin	Antidep Tryptomer Anafranil Prothiaden depnon	75-300 75-300 75-300 75-300 30-120
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine Sertraline	Fludac Serenata	10-80 50-200
Dopaminergic antidepressants	fluvoxamine	faverin	50-300
Atypical antidepressants	amineptine	survector	100-400
Monoamine oxidase inhibitors (MAOIs)	Trazodone isocarboxazid	Trazalon Marplan	150-600 10-30

Indications

- Depression: other psychiatric disorders
- Depressive:panic attack
- Episode
- Dysthymia: Generalized anxiety disorder
- Depression: Agrophilia, socialphobia
- Secondary Depression: Obsessive compulsive disorder with or without depression
- Abnormal grief reaction: Eating Disorder.

Pharmacokinetics:

- Antidepressants are highly lipophilic and protein bound. The half life is long and usually more than 24hrs.
- It is predominantly metabolized in the liver.

CONTRAINDICATIONS:

- Antidepressants are given with caution to patients because they cause arrhythmias.
- They increase symptoms of psychosis and mania in causes of mania-depressive psychosis.
- Drugs are given with caution to prevent liver disorders.

SIDE EFFECTS:

- Allergic side effects, Agranulocytes, cholestatic, skin rashes, systemic vasculitis.
- Metabolic and endocrine side effects: weight gain

MOOD STABILIZING DRUG

➔ Mood stabilizers are used for the treatment of bipolar affective disorders. some commonly used mood stabilizers are:

1.Lithium
2.carbamazepine
3.sodium valproate

LITHIUM

DESCRIPTION: It was discovered by Johan August Cade in 1949 and is a most effective and commonly used drug in the treatment of mania.

MODE OF ACTION:

- The probable mechanism of action can be: It accelerates presynaptic reuptake and destruction of catecholamines like norepinephrine; it inhibits the release of catecholamines at the synapse it decreases postsynaptic serotonin receptor sensitivity . All these actions result in decreased catecholamine activity, 6 ameliorating mania.

INDICATIONS:

➔ Acute Mania
➔ Prophylaxis For Bipolar And Unipolar Mood Disorder.
➔ Schizoaffective Disorder
➔ Cyclothymia

Impulsivity And Aggression

Other Disorders:

- Premenstrual Dysphoric Disorder
- Borderline Personality Disorder
- Trichotillomania
- Cluster Headaches

PHARMACOKINETICS:

★ ABSORPTION: Lithium Is Readily Absorbed With Peak Plasma Levels Occurring 2-4 Hrs After a Single Oral Dose Of Lithium Carbonate.
★ DISTRIBUTION**:** Lithium Is Distributed Rapidly In Liver And Kidney More Slowly In Muscle, Brain And Bone. Study State Levels Or Achieved In About Seven Days.
★ ELIMINATION**:** Elimination Is Predominantly Via Tubules And Is Influenced By Sodium Balance.
★ Depletion Of Sodium Can Precipitate Lithium Toxicity.

DOSAGES;

➔ Lithium is available in the market in the form of the following preparation:

- Lithium carbonate is 300 mg Example; licab 400 MG sustained release tablets.
- Lithium citrate;300mg/5ml liquid.
- Therapeutic level;0.8-1.2m Eq/L[for treatment of acute mania]
- Prophylactic levels=0.6 -1.2mEq/L【for prevention of relapse in bipolar disorder】
- Toxic lithium levels >2.0mEq/L

SIDE EFFECTS:

➔ Neurological: Tremors, motors hyperactivity; muscular weakness; seizures, neuro toxicity [delium, abnormal involuntary movements, seizures, coma].
➔ Cardiovascular wave depression.
➔ Gastrointestinal; Nausea, vomiting, diarrhea, abdominal pain and metabolic test
➔ Endocrine; abnormal thyroid function, goitre and weight gain.

SIDE EFFECTS DURING PREGNANCY AND LACTATION;

- Teratogenic possibility, Increased incidence of Epstein's anomaly distortion and downward displacement of tricuspid valve in right ventricle when taken in first trimester secreted in milk and causing toxicity in infants .

SIGNS AND SYMPTOMS OF LITHIUM TOXICITY

➔ Ataxia
➔ Coarse Tremor

- ➔ Nausea And Vomiting
- ➔ Impaired Memory
- ➔ Muscle Weakness
- ➔ Convulsions
- ➔ Coma

Confusion

CONTRAINDICATIONS OF LITHIUM:

- ❖ Cardiac ,Renal , Thyroid Or Neurological Dysfunctions.
- ❖ Presence Of Blood Dyscrasias
- ❖ Severe Dehydration
- ❖ Hypothyroidism
- ❖ History Of Seizures

CARBAMAZEPINE

Description:

It is variable in the market under different trained names like Manzetol, zeptol and Zen retard.

Mechanism of action:

- The stabilizing mechanism is not clearly established.
- Its antique Convulsant action may however be by decreasing synaptic transmission in the Central nervous system.

Indications;

- ➢ Seizures-Complex Partial Seizures, Gastrointestinal Tract. Complex Seizures Due To Alcohol Withdrawal.
- ➢ Psychiatric Disorders- Rapid Cycling, Bipolar Disorder, Acute Depression Impulse Control Disorder, Aggregation
- ➢ Psychosis With Epilepsy: Schizoaffective Disorders, Borderline Personality Disorder, Cocaine Withdrawal Syndrome.
- ➢ Paroxysmal Pain Syndromes -Trigeminal Neuralgia And Phantom Limb Pain.

Dosage;

- The average daily dose is 600 to 1800 MG oral in divided doses.The therapeutic blood levels or 16 to 12 UG per ml toxic blood levels or attained at more than UG per/ml.

Side effects;

- Drowsiness
- headache
- Depression
- jaundice
- leucopenia

SODIUM VALPROATE:

Mechanism of action;

- The drug acts on gamma aminobutyric acid [GABA]gamma aminobutyric acid [GABA] an inhibitory amino acid neurotransmitter.
- GABA receptor activation serves to reduce neuronal excitability.

Indication:

- Acute mania
- prophylactic treatment of bipolarI disorder
- Rapid cycling bipolar disorder
- Schizoaffective disorder
- Seizures

Other disorders:

- Bulimia
- nervosa
- obsessive-compulsive disorder, agitation and PTSD.

Dosage:

- ➔ The usual dose is 15mg/kg/day with a maximum 600 mg kg/day orally .

Side effects:

- Nausea
- vomiting
- Diarrhea
- Ataxia
- Tremor
- Loss of hair
- Weight Gain
- Loss Of Hair
- Thrombocytopenia
- Platelet Dysfunction

Anti Agents including sedatives and Hypnotics:

Description:

- Anxiety is a state which occurs in all human beings at some time or other.
- It is also a cardiaterial symptom of many psychiatric conditions.
- The drugs used to relieve anxiety are called anxiety or antianxiety or anxiolytic agents.
- Anti-Anxiety drugs relieve moderate to severe anxiety and tension.

Mode of action;

- These non-barbiturate benzodiazepines act as CNS depressants.
- It is believed that these drugs increase or help the inhibitory neurotransmitter action of gamma-aminobutyric inhibitor in all areas of CNS So, there is inhibition or control on the cortical and limbic system of brain, which is responsible for emotions such as range and anxiety.

Indications;

o For control of alcohol withdrawal symptoms.
o To control convulsions.
o To produce skeletal muscle relaxation.
o To provide short- term sleep preoperatively prior to diagnosis and insomnia.

Contraindications:

- Patients with renal or liver and respiratory impairment are given anti-anxiety drugs with caution.

CLASSIFICATION OF ANTIANXIETY AGENTS:

CHEMICAL GROUP & GENERIC NAME	TRADE NAME	RANGE OF DAILY DOSAGE IN mgm	ACTION
I.Non-Barbiturates **A.Benzodiazepines** ● Chlordiazepoxide ● Diazepam ● Oxazepam ● Prazepam ● Clorazepate ● Flurazepam ● Nitrazepam ● Lorazepam **B.Non-Benzodiazepine Propanediols** ● Meprobamate	Librium, Equibrome Valium. Calmpose Serepax Verstran Tranxene Azene Dalmane Nitravet Mogadon ativan Equanil Miltown Tybamate	15-100 6-50 30-120 20-60 11.25-60 15-60 10-30 2-6 1.2-1.6 1.2-1.6 1.2-1.6	These are nonbarbiturate benzodiazepines. They produce a tranquilizing effect without much sedation.These drugs are potential for abuse. These drugs have sedative action & present a high risk of abuse & physical dependance.
II.Antihistamines ● Hydroxyzine	Atarax vistaril	30-200 30-200	

CLASSIFICATION OF SEDATIVES AND HYPNOTICS:

CHEMICAL GROUP & GENERIC NAME	TRADE NAME	HYPNOTIC DOSE RANGEDAILY IN mgm	SEDATIVE DOSE DAILY IN mgm	ACTION
III.Barbiturates ● Amobarbital SA ● Butabarbital SA ● Pentobarbital LA ● Phenobarbital LA ● Thiopental USA	Amytal Butisol Nembutal Luminal pentothal	100-200 100-200 100-200 100-200 Used for anesthesia	60-150 20-200 60-150 30-90	These druga cause drowsiness lethargy,decreased alertness & sleep.Tolerance to drug can occur within 7-14 days,resulting in physical dependance.
IV.Nonbarbiturates				
V. Quinazolines ● Methaqualone	Quaalude Parest Optimal Mandrax	150-300	250-300	
VI.Acetylenic Alcohols ● Ethchlorvynol	Placidyl	0.5gm-1 gms	200-600mgm	
VII.Chloral Derivatives ● Chloral hydrate ● Chloral betaine	Noctaec Beta-chlor	0.5gm-2gms 870mg-1gm		
VIII.Monoureides				

Side effects of anti anxiety sedatives and hypnotics:

Central nervous system:

- Drowsiness
- Ataxia
- confusion
- depression
- blurred vision
- Rashes of skin

NOVEL DRUGS USED IN THE TREATMENT OF PSYCHOPHARMACOLOGY

BRILAROXAZIN【RP5063】OR ARIPIPRAZOLE

➔ **Class:** Brilaroxazine belongs to a class of third generation antipsychotics called dopamine-serotonin system stabilizers.

➔ **Approved date:** 25/5/23

➔ **Indication**:Treatment of schizophrenia schizoaffective disorder, Idiopathic pulmonary fibrosis major depressive disorder.

Mechanism of action:

- It activated activity of a demonstrated activity of a partial agonist D2,D3,D4 receptors,and serotonin 5Ht1A and 5Ht2A receptors with antagonistic activity on serotonin 5HT1B,5HT6 and 5HT7 receptors.
- Initial clinical experience in healthy volunteers and patients with schizophrenia and schizoaffective disorder define this molecule as a promising addition to current pharmacological modalities.

Dosage form ; Single dose 50 mg once daily for 28 days.

Pharmacokinetics:

➔ These studies provided for an initial assessment of the pharmacokinetic profile. In the single dose study,plasma concentrations of brilaroxazine peaked at about 5 hrs after dosing and then declined in a biphasic manner with a terminal half life of approximately 40 to 50 hrs. Mean c max and area under the curve[AUC]increase in linear,dose proportion fashion over the dosing range

Pharmacodynamics:

➔ Brilaroxazine acts as a potent partial agonist of D2, D3, D4 and 5-HT1A receptors, and as an antagonist of 5-HT2A, 5-HT2B, 5-HT2C, 5-HT6 and 5-HT7 receptors.Brilaroxazine exhibits high affinity for D2S, D2L, D3, D4.4, 5-HT1A, 5-HT2A, 5-HT2B, 5-HT7 and H1 receptors, and moderate affinity for D1, D5, 5-HT2C, 5-HT3, 5-HT6 and α4β2 nicotinic receptors, the serotonin transporter, and the α1B adrenergic receptor. It lacks significant affinity for 5-HT1B, α2 adrenergic, and muscarinic acetylcholine receptors, as well as for the norepinephrine and dopamine transporters.

Uses :

➔ Used in the treatment of schizophrenia,schizoaffective disorder idiopathic pulmonary fibrosis is a major depressive disorder.

Name : CARIPRAZINE

Class : it is currently used to treat schizophrenia and depressive disorders associated with bipolar-1 disorder

Approved date:16/12/22

Indication:

➔ Cariprazine is indicated for the treatment of schizophrenia in adults to manage both positive and negative symptoms. It is also indicated in monotherapy for acute management of manic or mixed episodes associated with bipolar I disorder (bipolar mania) in adults, and acute management of depressive episodes associated with bipolar I disorder (bipolar depression) in adults.

Dosage;1.5 mg

Mechanism of action:

➔ Cariprazine is not fully elucidated. Cariprazine potently binds to both of these receptors, more preferably to D3 receptors with higher affinity

pharmacokinetics:

➔ The pharmacokinetic properties of cariprazine are characterized by relatively slow absorption, multiexponential disposition,and slow elimination.

pharmacodynamics:

➔ Cariprazine produces two clinically relevant metabolites: desmethyl-cariprazine and didesmethyl-cariprazine, the latter having a longer half-life than cariprazine. Hello hello Exposure to didesmethyl-cariprazine exceeded that of the parent drug. Cariprazine is metabolized by CYP3A4 and to a lesser extent by CYP2D6.

Contraindications:

➔ VRAYLAR is contraindicated in patients with history of hypersensitivity reaction to cariprazine

Drug interactions:

➔ caprizone is combined with Acenocoumarol.

Side effects:

- Extreme Tiredness
- Restlessness
- Anxiety
- Agitation

- Difficulty In Falling Asleep Or Staying Asleep
- Increased Appetite

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