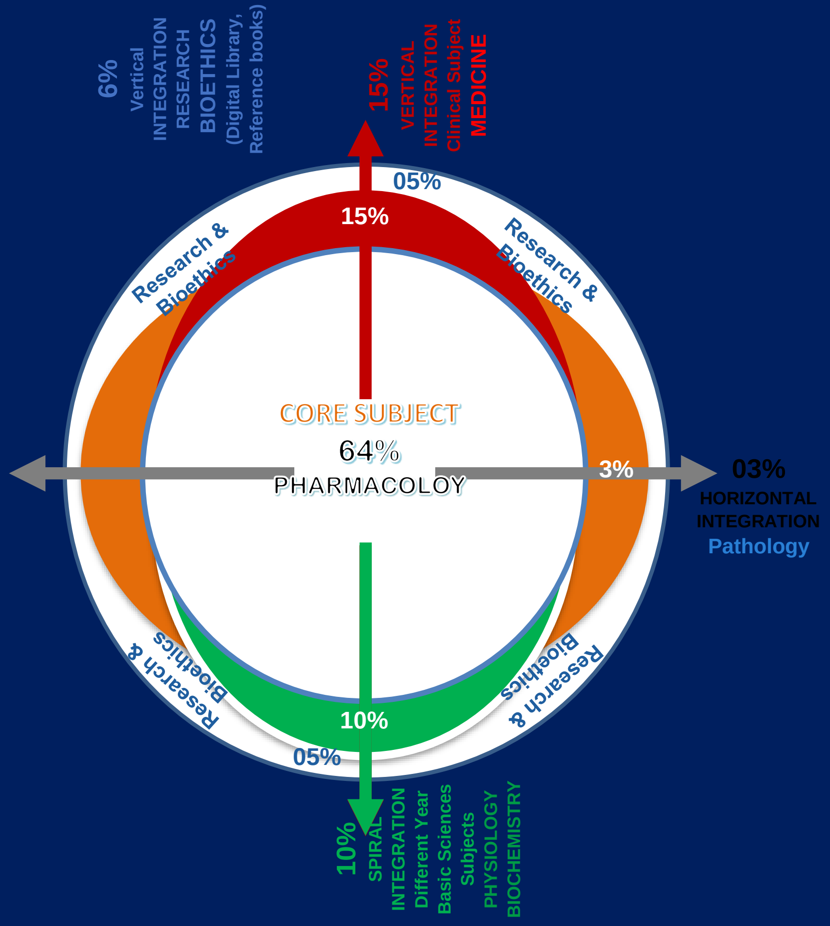

بسم الله الرحمن الرحيم

# MOTTO AND VISION VI


- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

# Prof Umar's Clinically Oriented Integrated Model For Basic Sciences And Interactive Lecture




| 4th Year Pharmacology LGIS | | |
|---|---|---|
| Core Subject – 64% | | |
| Pharmacology | | |
| Horizontal Integration – 3% | | |
| Same Year Subjects | • | Pathology (2) |
| Vertical Integration – 6% | | |
| Clinical Subjects | • | Medicine (3) |
| Spiral Integration – 10% | | |
| Different Year Basic Sciences Subjects | •<br>• | Physiology<br>Biochemistry |
| Research & Bioethics,Digital library 9% | | |
| | | |

# Anti-psychotic Drugs

# Psychosis

"Illness characterized by disturbance of reality and perception, impaired cognitive functioning, and disturbances of affect or mood"

- Positive symptoms……..delusions / hallucinations / thought disorders / abnormal disorganized behavior / catatonia
- Negative symptoms……..withdrawal from social contacts / flattening of emotional responses / anhedonia / reluctance to perform everyday tasks
- Cognitive deficit symptoms……..deficits in cognitive functions (e.g memory, attention)

# Adverse effects

ANTI PYCHOTIC AGENTS

- Neurological effects
- Metabolic & Endocrine effects
- Neurolept malignant syndrome
- Cardiac Toxicity
- Behavioural effects
- Autonomic nervous system

## Adverse Effects

- Neurological Effects
  - Extrapyramidal reactions
    - Parkinson's syndrome, akathisia, acute dystonic reactions
    - Antimuscarinics / antihistamines (diphenhydramine)
  - Tardive dyskinesia
    - Abnormal choreoathetoid movements
    - Relative cholinergic deficiency secondary to supersensitivity of DA rec. in caudate-putamen
    - Typical (20 – 40%) / Risperidone & paliperidone
    - Early detection……….reversal
    - Management
      - Dose reduction / switching to atypical (quetiapine or clozapine)
      - Withdrawal of drugs with antimuscarinic effect (TCAs, antimuscarincs for PD)
      - Diazepam
  - Seizures
    - Chlorpromazine / clozapine
    - Anticonvulsants

# Adverse effects

Neurological effects

Metabolic & Endocrine effects

Neurolept malignant syndrome

ANTI PYCHOTIC AGENTS

Cardiac Toxicity

Behavioural effects

Autonomic nervous system

## Adverse Effects

- Neuroleptic Malignant Syndrome
    - Life threatening extrapyramidal syndrome
    - Pathophysiology
        - Extreme sensitivity to DA rec. blockade……….excessive rapid DA rec. blockade
    - Symptoms & Signs
        - Marked muscular rigidity (lead pipe rigidity) / hyperthermia / tachycardia / HTN / Autonomic instability / tachypnea / altered mental status (delirium, confusion)
    - Biochemical
        - Leukocytosis / elevated muscle-type creatine kinase
    - Management
        - Antiparkinsonism drugs, muscle relaxant (BZD / Dantrolene)
        - General measures / cooling measures
        - Switching to atypical antipsychotics

# Adverse effects

Neurological effects

Metabolic & Endocrine effects

Neurolept malignant syndrome

ANTI PYCHOTIC AGENTS

Cardiac Toxicity

Behavioural effects

Autonomic nervous system

## Adverse Effects

- **Behavioral Effects**
  - Typical……..dosage timings
  - Pseudo-depression……….drug-induced akinesia (t/m antiparkinsonism drugs) / high dose
  - Confusional state……….antimuscarinic effects
- **Autonomic Nervous System Effects**
  - Urinary retention, constipation etc………..antimuscarinic effect
  - Postural hypotension, impaired ejaculation…………$\alpha$-adrenergic blockade
- **Cardiac Toxicity**
  - Thioridazine………T wave changes …….vent. Arrhythmias, torsades de pointes, cardiac conduction block, sudden death………Combination (antimuscarinics, tricyclic antidepressants)…………caution
  - Ziprasidone…………QT prolongation………Combination……….Thioridazine, Pimozide, Antiarrhythmics (1A / 3)
  - Clozapine……….myocarditis

# Adverse effects

**ANTI PYCHOTIC AGENTS**

- Neurological effects
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## Adverse Effects

- Metabolic and Endocrine Effects
  - Weight gain & Hyperlipidemia………clozapine / olanzapine………… caution
  - Hyperglycemia…………insulin resistance………..DM (clozapine / olanzapine)
  - Diabetic ketoacidosis
  - Risperidone / paliperidone / aripiprazole (less)……… Ziprasidone (least)……..Wt & Lipids
  - Risk of atherosclerotic cardiovascular diseases
  - Monitoring…………physical / biochemical (BSF, $HbA_{1C}$, lipid profile)
  - Hyperprolactinemia
    - Females………..amenorrhea / galactorrhea / infertility / osteoporosis
    - Males………..loss of libido / impotence / infertility
    - Atypical…………..Aripiprazole

## Adverse Effects

- Toxic or Allergic Reactions
  - Agranulocytosis……clozapine (1-2%)……..6–18 wks…….monitoring (weekly – 6m/ 3 wks)
  - Cholestatic jaundice / skin eruptions
- Ocular Complications
  - Deposits in cornea & lens……….chlorpromazine
  - Deposits in retina………..thioridazine……..browning of vision……..retinitis pigmentosa
- Dysmorphogenesis……….teratogenic risk……….neurodevelopment (NT)
- Overdosage
  - Thioridazine / mesoridazine
  - Drowsiness, miosis, agitation, convulsions, hypotension, vent. arrhythmias, hypothermia, coma
  - ABCD treatment…….airway, breathing, circulation, definitive t/m

## Drug Interactions

- Antimuscarinics / α-adrenergic blockers / antihistaminics

# Anti-psychotic Drugs

## Typical vs Atypical Antipsychotics

- Chemistry
- Mechanism of Action………..differences in receptor binding / affinity
- Therapeutic Efficacy…………e.g. Atypical………..negative symptoms
- Adverse Effects………Atypical
    - Less adverse effects: extrapyramidal, anticholinergic, endocrine effects, etc
    - Better tolerated
    - More patients compliance due to less untoward effects
- Cost-effectiveness……….Atypical

# Mood-stabilizing Drugs

# Bipolar Disorders

- Manic-depressive illness
- Manic phase / Depressive phase / Mixed symptoms / cognitive impairment
- Variable episodes……….mania / depression……..cycling of mood swings
- Risk of suicide

Pathophysiology

- Unknown………..strong familial component……..genetic
- Catecholamine-related activity………..Dopamine / NE / Glutamate

Treatment………….Mood-stabilizing Drugs

- Lithium
- Anticonvulsants……..Carbamazepine / Valproic acid / Lamotrigine / Gabapentin Oxcarbazepine
- Antipsychotics……….Aripiprazole / Chlorpromazine / Olanzapine / Quetiapine / Risperidone / Ziprasidone
- Olanzapine with Fluoxetine

# Lithium

- Mood-stabilizing Drug

**Pharmacokinetics**

- Absorption………complete
- Target plasma conc…………0.6 – 1.4 mEq/L
- Distribution……….total body water
- PPB & Metabolism……….None
- $t_{1/2}$………20 - 24 hrs
- Excretion…….PCT (80% - reabs)……..compete $Na^+$………$Li^+$ retention by $Na^+$ loss (e.g. diuretics)
- Feces / sweat / saliva / tears / breast milk

# Lithium

**Pharmacodynamics**

**Mechanism of Action**

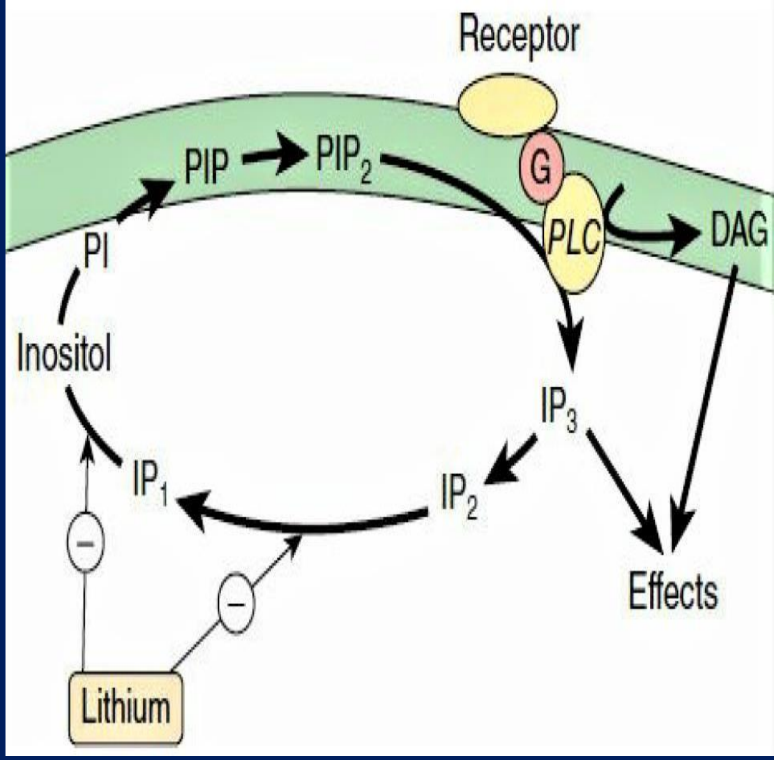
1. Effect on Electrolytes & Ion Transport
2. Effect on Signal Transduction
3. Effect on Gene Expression & Regulation

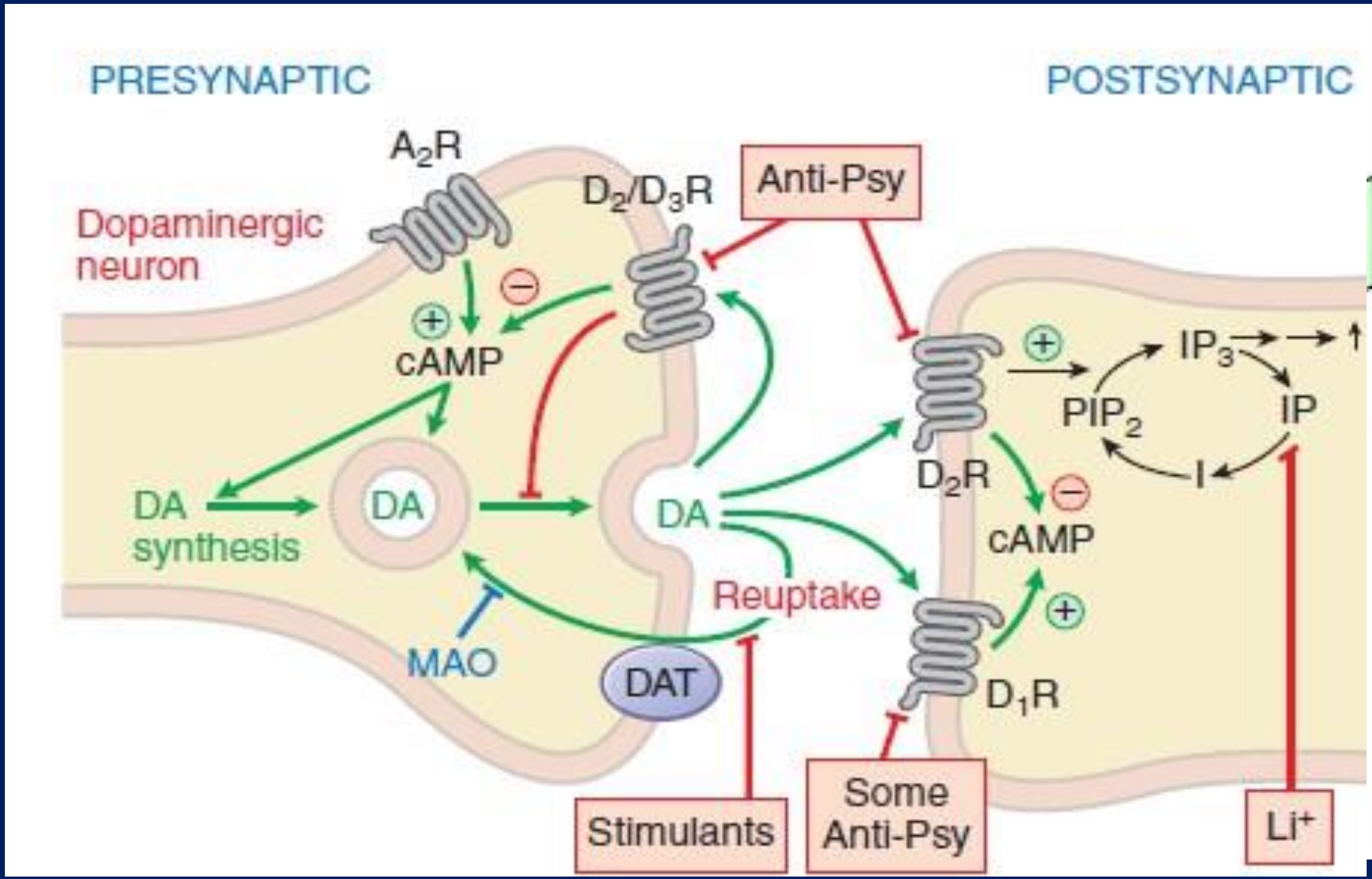
4. **Effect on Electrolytes & Ion Transport**
    - Develops small gradient across cell membrane
    - Substitute for $Na^+$
    - Not substrate for $Na^+$ -$K^+$ pump / $Na^+$ – $Ca^{++}$ exchanger
5. **Effect on Signal Transduction**
    a. Effect on Receptor-G protein interaction
        - Uncoupling of receptors from G protein
        - Vasopressin (ADH) receptors / TSH receptors

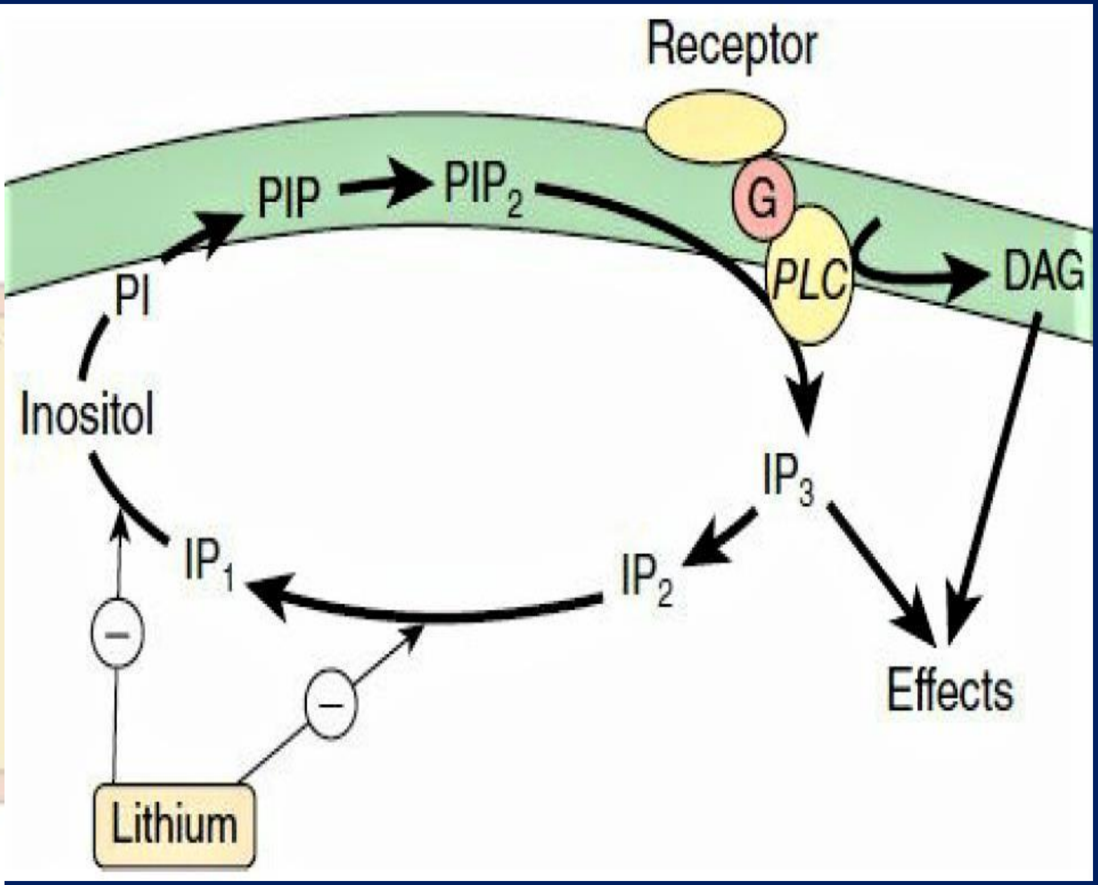
# Lithium

## b. Effect on Second Messenger Systems

- Phosphatidylinositol Pathway
  - Phosphatidylinositol (PI)…………membrane lipid
  - Recycling of membrane phosphoinositides**
  - Inhibits Inositol polyphosphate 1-phosphatase & Inositol monophosphatase
  - Decrease cerebral inositol levels
  - Mania………over-activity of the neurotransmitters pathways
  - Diminished effects of neurotransmitters involving $IP_3$-DAG pathway
  - Valproic acid & Carbamazepine…………Inositol depletion
- Adenylyl Cyclase
  - Inhibit NE sensitive AC




PRESYNAPTIC
POSTSYNAPTIC
A2R
D2/D3R
Anti-Psy
Dopaminergic neuron
cAMP
DA synthesis
DA
DA
Reuptake
MAO
DAT
D2R
D1R
cAMP
IP3
PIP2
IP
I
Stimulants
Some Anti-Psy
Li+


Receptor
G
PLC
PIP
PIP2
DAG
PI
Inositol
IP3
IP2
IP1
Effects
Lithium

# Lithium

c. Effect on Protein Kinases

- Decreased functioning of PK (esp. PKC) in brain
  - Excessive PKC activation…………behavioral dysfunction
  - Causes alteration in release of NT & hormones
  - Valproic acid

3. Effect on Gene Expression & Regulation

- Inhibit Glycogen synthase kinase-3 (GSK-3)
  - GSK-3 phosphorylates β-catenin………intracellular signaling pathway
  - Increased β-catenin……….transcription factors interactions
- Alteration in gene expression & protein production
- Alteration in Synaptic & Neuronal Plasticity
- Mood Stabilization

# Lithium

**Therapeutic Uses**

- Monitoring
- Maintenance t/m
- Bipolar Affective Disorders
- Recurrent Depression
- Schizoaffective Disorders
- Schizophrenia

# Lithium

**Therapeutic Uses**

- Monitoring……….Sample (10 – 12 hrs postdose)……….5 days………desired level
- Maintenance t/m……frequency / severity /pt comp./ residual damage…………0.6– 0.9 mEq/L
- Bipolar Affective Disorders
  - Slow onset………supplemented………BZD / antipsychotics………manic phase
  - Combination therapy…………maintenance therapy
  - Depressive phase……….Antipsychotics / Bupropion / Lamotrigine / SSRIs
  - Lithium……….prevention of both phases
- Recurrent Depression
  - With antidepressants (e.g. imipramine)
- Schizoaffective Disorders
  - Schizophrenic symptoms with depression or excitement
  - With antidepressants or antipsychotics
- Schizophrenia
  - With antipsychotics……….refractory cases

# Lithium

**Adverse Effects**

- Neurological & Psychiatric Effects
- Thyroid Functions
- Renal Effects
- Edema
- Cardiovascular adverse effects
- Use in Pregnancy
- Overdose

## Adverse Effects

- Neurological & Psychiatric Effects
  - Tremors……Propranolol / Atenolol
  - Neurological…Choreoathetosis, motor hyperactivity, ataxia,dysarthria, aphasia
  - Psychiatric……Mental confusion, withdrawal behavior
  - Discontinuation / Monitoring
- Thyroid Functions
  - Hypothyroidism / thyroid enlargement……monitoring TSH (6 – 12 m)
  - Uncoupling of TSH receptor for G protein
- Renal Effects
  - Nephrogenic Diabetes Insipidus

    Polydipsia /polyuria/ADH unresponsiveness (G-protein) /responds to Amiloride
  - Decreased GFR
  - Chronic interstitial nephritis
  - Minimal-change glomerulopathy with nephrotic syndrome
  - Avoid dehydration (increases $Li^+$ conc. in urine)
  - Monitoring………periodic RFTs

## Adverse Effects

- Edema
  - $Na^+$ retention
  - Weight gain
- Cardiac Adverse Effects
  - Bradycardia-tachycardia (sick sinus) syndrome……..C/I…………SA node suppression
  - T-wave flattening
- Miscellaneous
  - Weight gain………..30%
  - Transient acneiform eruptions………..temporary discontinuation
  - Folliculitis
  - Leukocytosis………Leucopoiesis………therapeutic application

## Adverse Effects

- Overdosage
  - Therapeutic overdose……...accumulation……..renal status / hydration / diuretics
  - > 2 mEq/L……….caution
  - Small ion……….dialyzed easily
- Use in Pregnancy
  - Increased $Li^+$ renal clearance during pregnancy……...reversal after delivery
  - Breast milk………..Lethargy, poor suck & moro reflexes, cyanosis, hepatomegaly
  - Dysmorphogenesis………..cardiac (Ebstein's anomaly)

## Drug Interactions

- Diuretics (thiazides)……...decrease $Li^+$ clearance (25%)……..dose adjustment
- NSAIDs (except aspirin / acetaminophen)……...decrease $Li^+$ clearance
- Neuroleptics……….more severe EPS on combining with $Li^+$

# BIOETHICS

- Minimize the risk of dependence
- Minimize the risk of harm by monitoring closely
- Ethical prescribing
- Maintain confidentiality
- Provide comprehensive care to patient

SPIRAL INTEGRATION

# ROLE OF AI IN USE OF ANTIPSYCHOTICS

- Personalized medicine
- Dosing optimization
- Symptoms tracking
- Adherence monitoring
- Side effect prediction, drug interactions alerts
- Patient education
- Behavioral interventions
- Clinical trials
- New drug development

SPIRAL INTEGRATION

# HOW TO ACCESS DIGITAL LIBRARY

- Go to the website of HEC National Digital Library.
- On Home Page, click on the INSTITUTES.
- A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
- Select your desired Institute.
- A page will appear showing the resources of the institution
- Journals and Researches will appear
- You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.


THANK
YOU