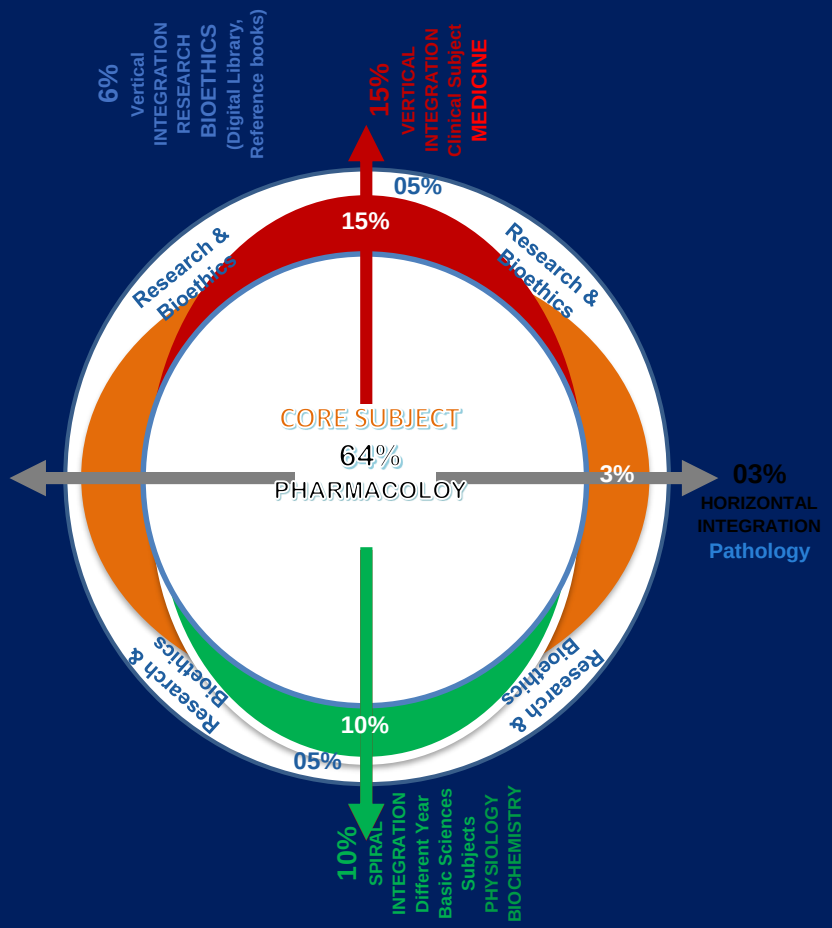

بسم الله الرحمن الرحيم

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	• Physiology • Biochemistry
Research & Bioethics,Digital library 9%	

Anti-psychotic Drugs

NG OBJECTIVES

Classify anti psychotic agents
Describe their mechanism of action
Discuss the pharmacokinetic and pharmacodynamics of all antipsychotic drugs
Explain the therapeutic uses with rationale
Name all adverse effects of antipsychotics

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)

Psychosis

Pathophysiology

- Organic basis / genetic / idiopathic
- Serotonin Hypothesis
  - Hallucinogens (LSD).....5-HT receptor agonist.....5-HT_{2A} & 5-HT_{2C}
  - 5-HT_{2A} modulate release.....DA / NE / GABA / Ach / Glutamate
  - 5-HT_{2A} stimulation.....depolarization of glutamate N & NMDA rec. stability
  - 5-HT_{2C} stimulation.....inhibit DA release
  - Antipsychotics.....Blockade / Inverse agonist

Psychosis

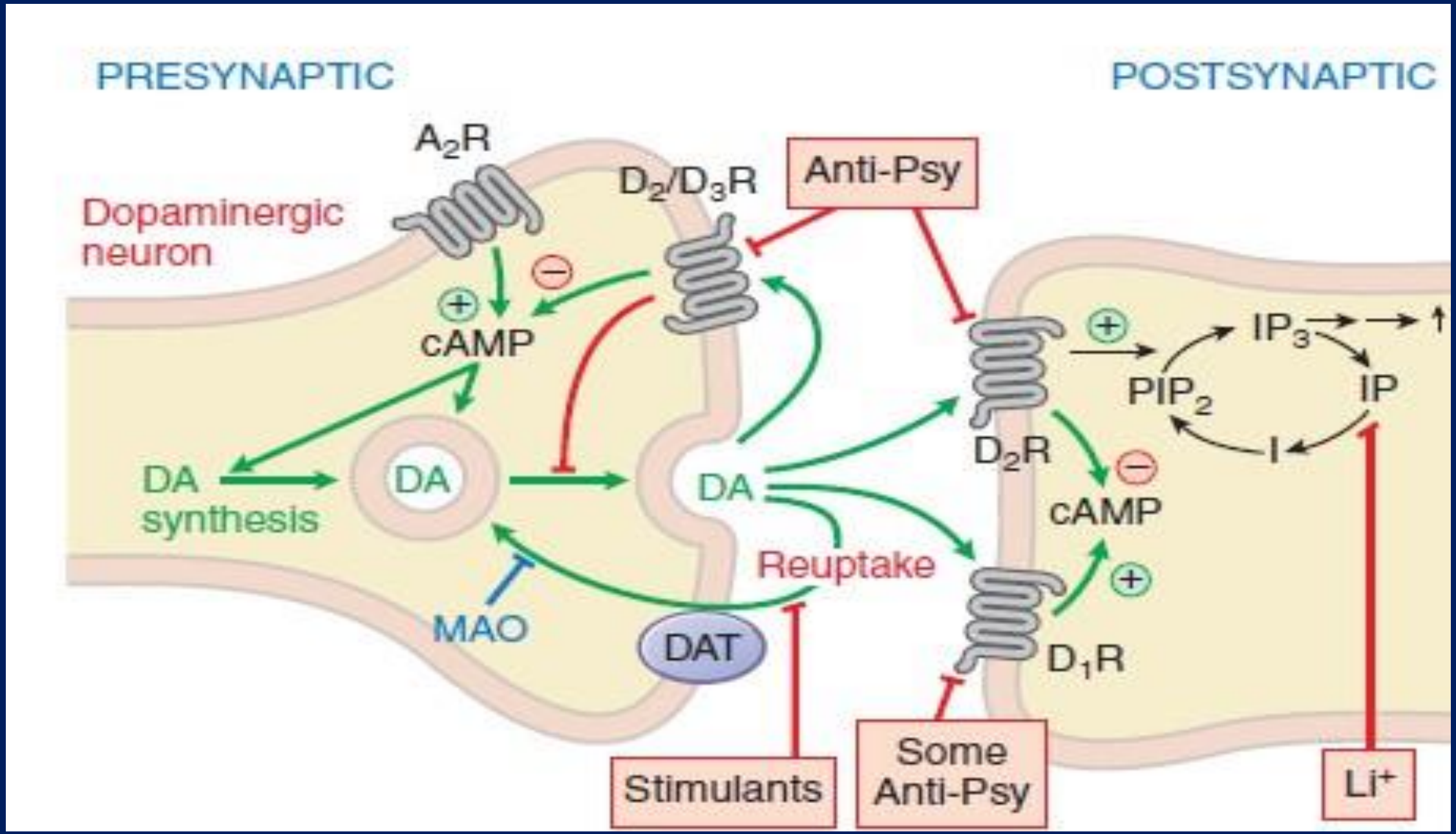
- Dopamine Hypothesis
  - Dopaminergic system effects
    - Mesocortical / Mesolimbic……Behavioral effects…….Psychosis (Schizophrenia)
    - Nigrostriatal…….Motor control…….Extrapyramidal effects (Parkinsonism)
    - Tuberoinfundibular…….Endocrine effects
    - Medullary-periventricular…….Eating behavior
    - Incertohypothalamic pathway
    - D_1-like rec (D_5)…… increase cAMP
    - D_2-like rec (D_3, D_4)……decrease cAMP…….antipsychotic & extrapyramidal effects

Psychosis

- **Dopamine Hypothesis**
  - Drugs or conditions enhancing dopaminergic activity (level or rec.)……psychotic s/s
  - Increased dopamine receptor density & dopamine levels
  - Reduced cortical & hippocampal dopaminergic activity……cognitive & negative symptoms
  - Atypical Antipsychotics……D_2 rec. blockade < 5-HT_{2A} rec. blockade

Psychosis

- **Glutamate Hypothesis**
  - Phencyclidine & Ketamine……..NMDA rec. blockade……..exacerbate psychosis
  - Hypofunctional NMDA rec. on GABAergic interneurons
  - GABAergic Inhibitory effect
  - Disinhibition of glutamatergic activity
  - Hyperstimulation of cortical neurons ……Psychosis
  - Glycine binding on NMDA rec. – not fully saturated


PRESYNAPTIC
POSTSYNAPTIC
Dopaminergic neuron
A_2R
D_2/D_3R
Anti-Psy
cAMP
DA synthesis
DA
DA
D_2R
IP_3
PIP_2
IP
I
cAMP
Reuptake
MAO
DAT
D_1R
Stimulants
Some Anti-Psy
Li^+

Anti-psychotic Drugs

CLASSIFICATION

FIRST GENERATION OR TYPICAL

- Phenothiazine Derivatives
  - Aliphatic Derivatives……Chlorpromazine
  - Piperidine Derivatives……Thioridazine
  - Piperazine Derivatives……Fluphenazine
    ……Perphenazine
    ……Trifluoperazine
- Thioxanthene Derivatives
  - Thiothixene
- Butyrophenone Derivatives
  - Haloperidol
  - Droperidol
- Miscellaneous
  - Molindone
  - Pimozide

Anti-psychotic Drugs

CLASSIFICATION

SECOND GENERATION OR ATYPICAL

- Clozapine
- Olanzapine
- Quetiapine
- Risperidone
- Paliperidone**
- Ziprasidone
- Aripiprazole
- Loxapine
- Sertindole
- Asenapine
- Zotepine
- Cariprazine
- Brexpiprazole

GLUTAMATERGIC ANTIPSYCHOTICS (Investigational)

- Bitopertin
- Sarcoserine

Anti-psychotic Drugs

PHARMACOKINETICS

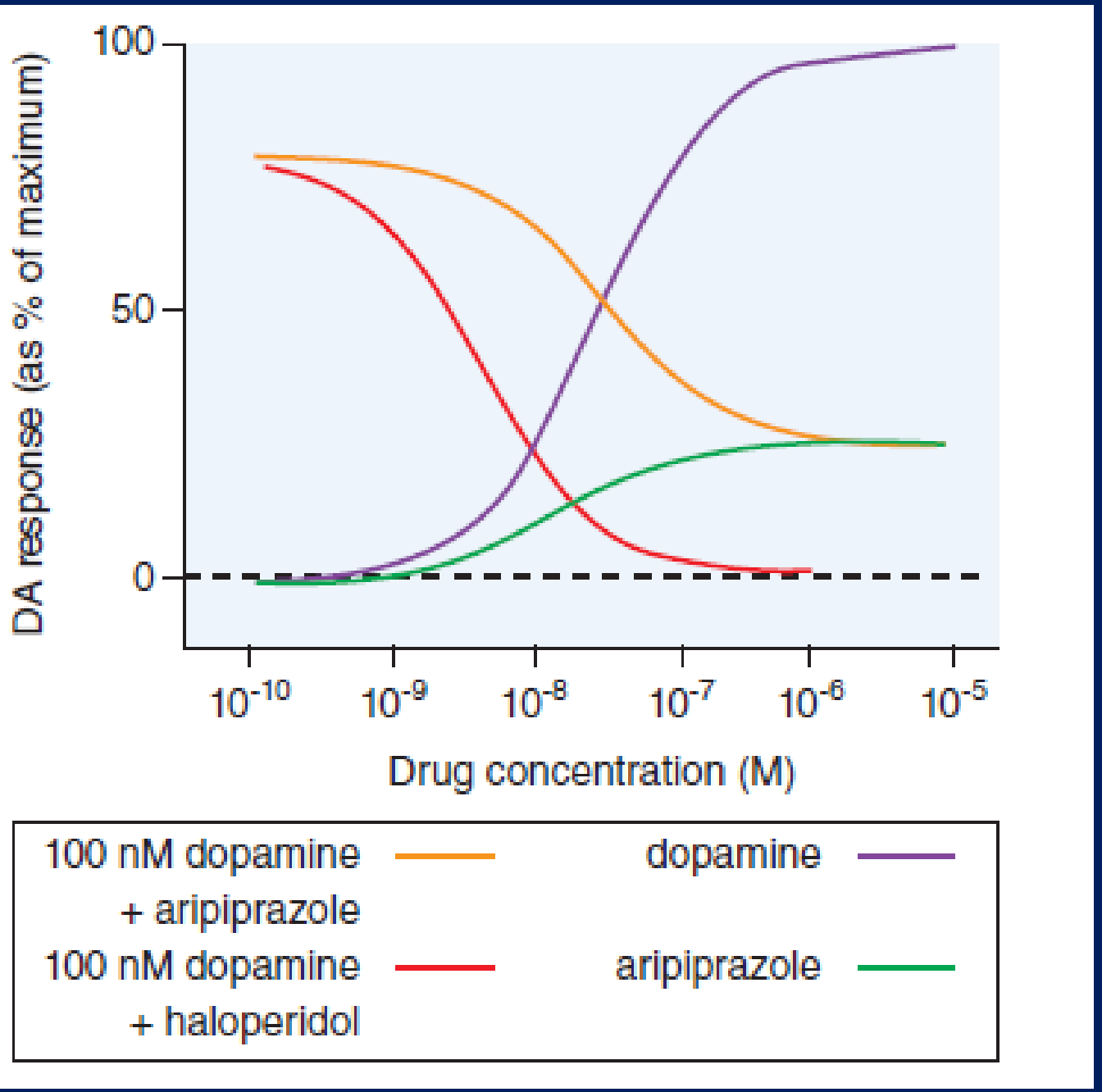
- **ROA…….oral / intramuscular / slow-release depot preparation**
- **Parenteral & depot formulations…….Fluphenazine / Haloperidol / Risperidone / Paliperidone / Olanzapine / aripiprazole**
- **FPM / PPB / lipophilicity / distribution**
- **Metabolism…….CYP3A4 / CYP2D6 / CYP1A2**
- **Excretion**
- **$t_{1/2}$ vs DOA (receptor occupancy)…….e.g. long acting injectable formulation**
- **Variable time for relapse (exc. Clozapine)**

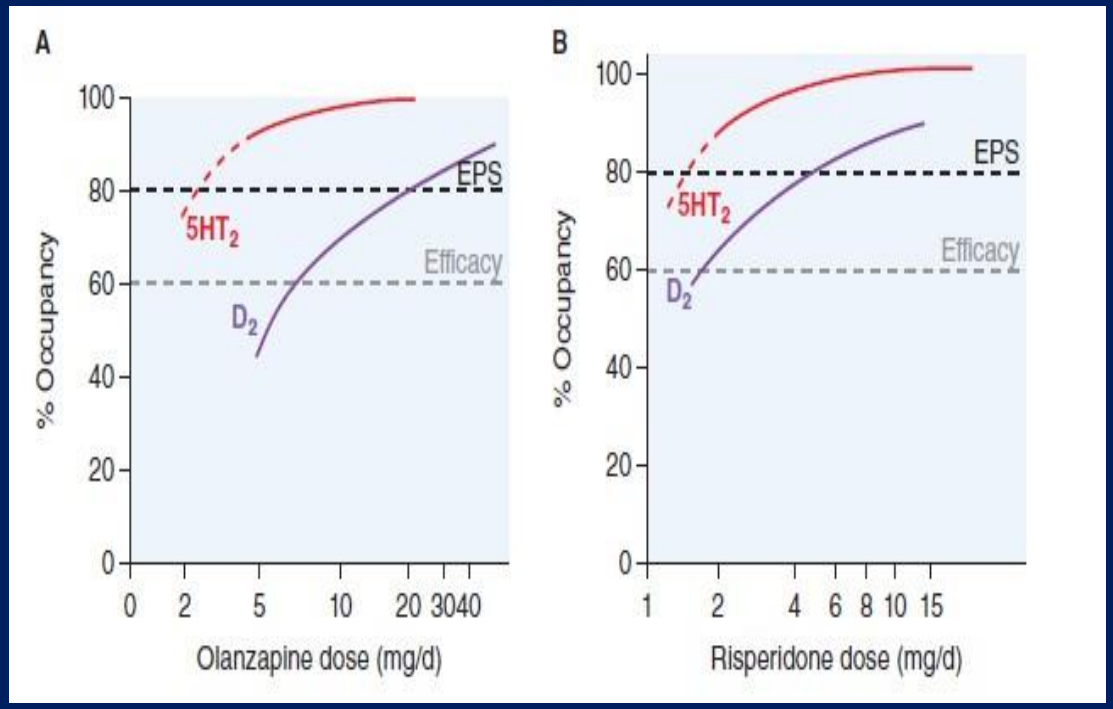
Anti-psychotic Drugs

PHARMACODYNAMICS

Mechanism of Action

- Most of typical & some atypical……D_2 rec. antagonist
- Most of atypical & some typical……5-HT_{2A} rec. antagonist
- Relative rec. affinity / blockade
- Extrapyramidal effects……80% D_2 rec. occupancy
- Neuroleptic……high incidence of EPS
- D_1 & D_3 / 5-HT / α-adrenergic / muscarinic / H_1 histamine rec……additional & side effects
- Clozapine & Olanzapine……5-HT_{2A} rec. antagonist
- Aripiprazole……partial agonist of D_2 & 5-HT_{1A} rec. / Antagonist of 5-HT_{2A} rec.
- Cariprazine…… Antagonist of D_2 & 5-HT_{2A} rec. / Partial agonist of D_3 rec.
- Glutamatergic Antipsychotics (Bitopertin & Sarcoserine)……GlyT1 inhibitors


100
50
0
DA response (as % of maximum)
10^{-10}
10^{-9}
10^{-8}
10^{-7}
10^{-6}
10^{-5}
Drug concentration (M)
100 nM dopamine + aripiprazole
dopamine
100 nM dopamine + haloperidol
aripiprazole



Chlorpromazine: α1 = 5-HT2A > D2 > D1

Haloperidol: D2 > α1 > D4 > 5-HT2A > D1 > H1

Clozapine: D4 = α1 > 5-HT2A > D2 = D1

Olanzapine: 5-HT2A > H1 > D4 > D2 > α1 > D1

Aripiprazole: D2 = 5-HT2A > D4 > α1 = H1 >> D1

Quetiapine: H1 > α1 > M1,3 > D2 > 5-HT2A

Anti-psychotic Drugs

PHARMACOLOGICAL EFFECTS

Psychological Effects

- Nonpsychotic……..unpleasant subjective effects & impaired performance
- Akathisia, sleepiness, restlessness, autonomic effects
- Psychotic…….Improved behavior, performance & cognition
- Extrapyramidal effects…….mild to severe
- Sleep promoting effect……low dose (esp. quetiapine)

Electroencephalographic (EEG) Effects

- EEG frequencies & amplitude……slowing (focal or unilateral) / increased synchronization
- Decrease seizure threshold……seizure-like EEG pattern……caution in epileptic patient

Anti-psychotic Drugs

PHARMACOLOGICAL EFFECTS

Endocrine Effects

- Tuberoinfundibular……Endocrine effects
- Typical, risperidone & paliperidone……Increased prolactin……S/E
- Atypical……minimal effect……prolactin & EPS

Cardiovascular Effects

- Phenothiazines……Decreased BP (postural), PVR, stroke vol……Increased HR
- Thioridazine……QT interval / abnormal configuration of ST segment & T wave
  ……torsades de pointes……second line drug
- Atypical (sertindole, ziprasidone, quetiapine)……QT interval prolongation
- Atypical……Metabolic syndrome with increased risk of CAD, stroke, HTN

TABLE 29–2 Adverse pharmacologic effects of antipsychotic drugs.

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α-Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine-receptor blockade
	Tardive dyskinesia	Supersensitivity of dopamine receptors
	Toxic-confusional state	Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H_1 and 5-HT_2 blockade

Anti-psychotic Drugs

Therapeutic Uses

Psychiatric Indications

- **Schizophrenia**
  - **Catatonic form……BZD (I/V)……antipsychotics**
  - **Negative symptoms……atypical**
  - **Refractory case……Clozapine / olanzapine……6 months**
  - **Reduce suicidal tendency……Clozapine**
- **Schizoaffective disorders**
  - **Antipsychotics / antidepressants / Lithium / Valproic acid**

Anti-psychotic Drugs

Therapeutic Uses

Psychiatric Indications

- Schizophrenia
- Schizoaffective disorders
- Bipolar affective disorder
  - Manic phase
    - Antipsychotics / Lithium / Valproic acid / BZD (e.g. Lorazepam, clonazepam)
  - Depressive phase…….Psychotic depression
    - Antipsychotics (aripiprazole / quetiapine / clozapine) with antidepressants (fluoxetine)
  - More effective in manic phase

Anti-psychotic Drugs

Therapeutic Uses

Psychiatric Indications

- **Agitation**
  - **Schizophrenia / Bipolar affective disorder / delirious or post surgical patients**
  - **Haloperidol / ziprasidone / aripiprazole……I/M**
- **Unipolar depression……Adjunctive use with antidepressants**
- **Non-maniac excited states……BZD / Antipsychotics**
- **Alzheimer's disease……disturbed behavior**
- **Tourette's syndrome**

Anti-psychotic Drugs

Therapeutic Uses

Non-psychiatric Indications

- **Antiemetic**……typical (exc. Thioridazine)…….D_2 rec. antagonist…….Prochlorperazine
- **Relief of Pruritus**……phenothiazines…….H_1 rec. antagonist
- **Preoperative sedative**…….promethazine(Phenergan)
- **Neuroleptanesthesia**…….Droperidol + Fentanyl + Nitrous oxide

Anti-psychotic Drugs

Therapeutic Uses

Choice of Drug and Dosage

- Differences in efficacy / adverse effects
- Oral / Parenteral & depot formulations (LAI)
- Titration to an effective dose……broad TI
- Patient characteristics
- Patient past response……Switching of drugs
- Cost-effectiveness……generic forms……aripiprazole

Drug Combinations

- Antidepressants / BZD / Lithium / Valproic acid / ECT

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

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.

SPIRAL INTEGRATION

FURTHER READING

•Cho J, Spence MM, Niu F, Hui RL, Gray P, Steinberg S. Risk of overdose with exposure to prescription opioids, benzodiazepines, and non-benzodiazepine sedative-hypnotics in adults: a retrospective cohort study. Journal of general internal medicine. 2020 Mar;35:696-703.

•Sweetman A, Putland S, Lack L, McEvoy RD, Adams R, Grunstein R, Stocks N, Kaambwa B, Van Ryswyk E, Gordon C, Vakulin A. The effect of cognitive behavioural therapy for insomnia on sedative-hypnotic use: A narrative review. Sleep medicine reviews. 2021 Apr 1;56:101404.

SPIRAL INTEGRATION


THANK
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