

Systemic Pharmacology II

BP506T

A Textbook for B.Pharm Semester V

As per the new PCI Syllabus 2026 (NEP 2020)

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Course Code: BP506T

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Preface

Systemic Pharmacology II occupies a decisive place in the B.Pharm programme. It is where the student stops learning drugs one receptor at a time and begins to think in whole systems: how a single class of molecules can quiet a seizing brain, how selective toxicity lets one drug kill a microbe while sparing its host, how a hormone taken as a tablet reshapes metabolism. The BP506T syllabus gathers four such systems, the central nervous system, chemotherapy, the endocrine glands, and the gastrointestinal tract, and asks the student to master both the mechanisms and their clinical use.

This book is written to that end. Every class of drug is taught from its definition and classification, through the mechanism of action derived rather than merely asserted, to its therapeutic uses and the adverse effects that examinations and clinics test. The account is formal and dense, but it is written to be read and understood, not merely revised.

Comparison tables open each classification, original figures make the mechanisms visible, and a graded self-assessment closes every chapter so that the reader can test recall, application, and analysis.

The material has been checked against the standard references named in the syllabus, in their current editions.

Where a topic is simplified to make it learnable, the simplification is signalled rather than hidden, so that it does not harden into a misconception.

The aim throughout has been a book that serves three readers from the same pages: the first-time learner meeting a class for the first time, the reviser consolidating before an internal examination, and the student reading the night before the university paper.

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Course Objectives

The objectives of this course are to:

1. Understand the neurohumoral transmission in the central nervous system and the role of neurotransmitters and their modulators in CNS disorders.
2. Learn the pharmacology of drugs used in pathological conditions of the CNS, GIT, and endocrine system.
3. Familiarize learners with the concepts of drug abuse, addiction, dependence, tolerance, and their management.
4. Impart comprehensive knowledge of chemotherapeutic agents including anticancer drugs.
5. Introduce the principles of rational use of chemotherapeutic agents.

Course Outcomes

On successful completion of this course, the student will be able to:

CO	Course Outcome
CO1	Identify the role of neurotransmitters in CNS diseases and explain the pharmacology of drugs acting on central neurotransmission.
CO2	Apply the principles of chemotherapy to explain the mechanisms and uses of chemotherapeutic agents.
CO3	Recall the pharmacology of hormones and drugs used in endocrine disorders.
CO4	Describe the mechanisms and therapeutic uses of drugs acting on the gastrointestinal tract.
CO5	Recognize issues related to drug abuse, addiction, and dependence and their management.

Syllabus (BP506T)

Unit	Topics	Hours
I	Neurohumoral transmission in the CNS; general anaesthetics and pre-anaesthetics; local anaesthetics; sedative-hypnotics; alcohol and disulfiram; opioids and antagonists; antiepileptics; drugs for Parkinson's and Alzheimer's diseases.	10
II	Antipsychotics, antidepressants, anti-anxiety drugs, mood stabilizers, CNS stimulants and hallucinogens; substance abuse, drug addiction, and principles of de-addiction.	07
III	Principles of chemotherapy; antimicrobial agents (sulphonamides and cotrimoxazole, fluoroquinolones, penicillins and cephalosporins, macrolides and tetracyclines, linezolid, carbapenems and monobactams, chloramphenicol and aminoglycosides); chemotherapy of fungal, viral, helminthic, urinary, tubercular, leprosy, malarial, amoebic, and neoplastic diseases.	14
IV	Basic concepts of endocrinology; thyroid and antithyroid agents; parathormone, calcitonin, and vitamin D; insulin and oral hypoglycaemic agents; ACTH and corticosteroids; oral contraceptives; drugs acting on the uterus; PCOD.	10
V	Drugs used in peptic ulcer; drugs for constipation and diarrhoea; emetics and anti-emetics; digestants, carminatives, appetizers, and anorectics.	04

Chapter 1: Neurohumoral Transmission in the CNS

Learning outcomes

After studying this chapter the student will be able to:

1. Define neurohumoral transmission and contrast central with peripheral transmission (CO1).
2. State the criteria for a central neurotransmitter and distinguish it from a neuromodulator (CO1).
3. Differentiate ionotropic from metabotropic receptors and excitatory from inhibitory transmission, and explain the relevance of the blood-brain barrier (CO1).
4. Describe, for each major central neurotransmitter, its location or pathway, receptor subtypes and principal function (CO1).
5. Link each transmitter to the CNS disorder that arises when its signalling fails, and use that map to predict where a drug class acts (CO1).

Introduction

Neurohumoral transmission is the process by which one neuron communicates with another, or with an effector cell, through the release of a chemical messenger that crosses the synaptic cleft and acts on a specific receptor. In the CNS this relay is the substrate on which almost every centrally acting drug works, whether anaesthetic, antiepileptic, antidepressant or antipsychotic: each changes the amount of a transmitter at a synapse or occupies its receptor. The clinical question is simple, which chemical signal has failed and where: name it and the correcting drug class follows. That logic, transmitter to disorder to drug, organises the whole CNS unit.

Central versus peripheral transmission

Peripheral transmission is simple: few transmitters (chiefly acetylcholine and noradrenaline, US *norepinephrine*), one-to-one wiring to a defined effector, and a mostly predictable outcome. Central transmission differs in degree and in kind.

- The CNS uses a large transmitter set: fast amino acids (glutamate, GABA, glycine), monoamines (dopamine, noradrenaline, serotonin, histamine), acetylcholine, and many peptide co-transmitters.
- A single neuron integrates thousands of inputs; its output is the algebraic sum of excitatory and inhibitory signals, not a relay.
- The same transmitter has opposite effects at different receptors: glutamate is always excitatory, but noradrenaline may excite or inhibit by adrenoceptor.
- Central synapses are protected by the blood-brain barrier, so a drug reaches them only if it can cross, a constraint absent at the periphery.

Selectivity is harder centrally: one transmitter serves many circuits, so a drug correcting one often disturbs another, producing the characteristic adverse effect.

Criteria for a central neurotransmitter

A compound qualifies as a central neurotransmitter only when it meets an established set of criteria.

- **Synthesised** in the neuron, the synthetic enzymes present in the terminal (e.g. glutamic acid decarboxylase for GABA).
- **Stored** in the presynaptic terminal (usually vesicles) and **released** into the cleft on depolarisation, calcium-dependent.
- Applied exogenously, it **mimics** the natural transmitter (identity of action).
- Its action is **terminated** rapidly, by reuptake or enzymatic degradation.
- Its effect is **blocked by a specific antagonist** that also blocks the response to nerve stimulation.

A substance that fails one or more of these tests yet still influences transmission is a neuromodulator.

Neuromodulators

A *neuromodulator* does not carry the primary fast signal but adjusts the strength of transmission mediated by a conventional transmitter, acting slowly and diffusely (often through metabotropic receptors) to set a synapse's gain rather than switch it on or off. Many peptides (e.g. substance P, enkephalins) and presynaptically-acting classical transmitters are modulators. The distinction is functional, not chemical: the same molecule can be transmitter at one synapse, modulator at another.

Ionotropic and metabotropic receptors

Central receptors fall into two families, governing how fast and how long a drug acts.

- **Ionotropic receptors** are ligand-gated ion channels (receptor and channel one protein): binding opens the pore within a millisecond, giving fast transmission. Examples: glutamate NMDA, AMPA, kainate; GABA-A; glycine.
- **Metabotropic receptors** are G-protein-coupled: the transmitter activates a G-protein and a second-messenger cascade (or a separate ion channel), so the response develops over milliseconds to seconds and outlasts the stimulus. Examples: dopamine and adrenergic receptors, most serotonin receptors, muscarinic receptors, GABA-B.

It is the receptor, not the transmitter, that sets the sign of the response: acetylcholine excites via nicotinic channels but slows the heart via muscarinic ones.

Excitatory and inhibitory transmission

Opening cation channels (Na^+ , Ca^{2+}) depolarises the membrane toward threshold, an excitatory postsynaptic potential (EPSP); opening Cl^- (GABA, glycine) or K^+ channels hyperpolarises it, an inhibitory postsynaptic potential (IPSP). Glutamate on AMPA and NMDA receptors is the chief excitatory event of the brain, GABA on GABA-A the chief inhibitory one (Table 1.1, Figure 1.1).

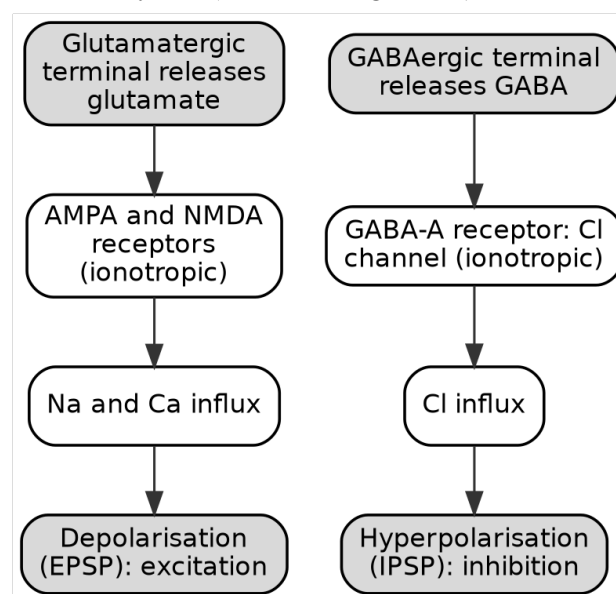


Fig 1.1: An excitatory glutamatergic synapse and an inhibitory GABAergic synapse, showing receptor type, ion movement and net effect.

The blood-brain barrier and its pharmacological relevance

The *blood-brain barrier* is formed by tight junctions between cerebral capillary endothelial cells, reinforced by astrocyte foot processes, and restricts passage of solutes from blood to brain.

- Only lipid-soluble, non-ionised, low-molecular-weight drugs cross by passive diffusion; polar or protein-bound drugs are largely excluded. Hence lipophilic thiopental induces anaesthesia within seconds while polar neuromuscular blockers act only peripherally.
- It dictates strategy: levodopa is given instead of dopamine because dopamine cannot cross, whereas levodopa crosses on an amino-acid transporter and is decarboxylated centrally.
- Efflux transporters such as P-glycoprotein pump many drugs back into the blood, lowering central concentrations.
- Inflammation (meningitis) loosens the barrier, raising central entry of drugs such as penicillins.

The major central neurotransmitters

Grouped by chemistry, they are fast amino acids, tone-setting monoamines, and acetylcholine (Figure 1.2).

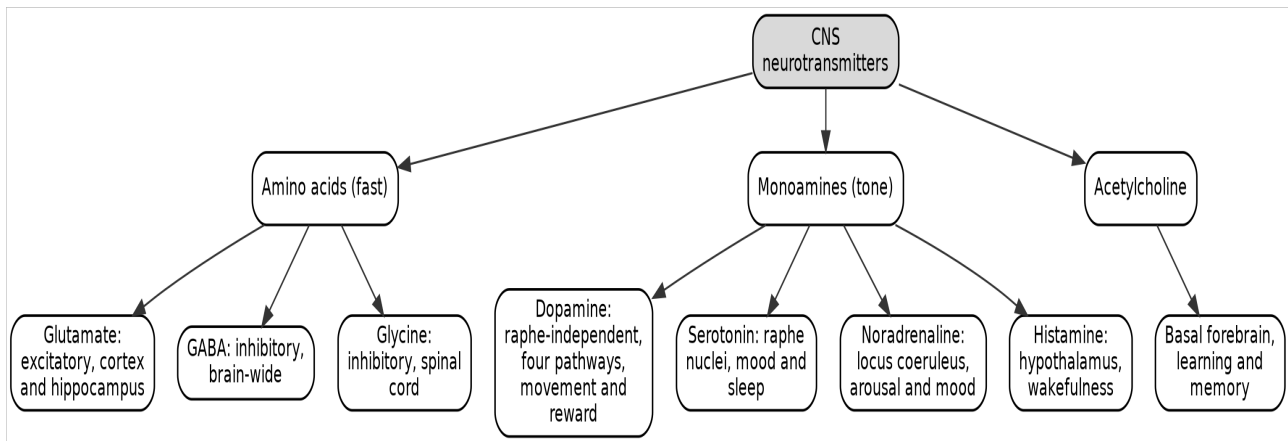


Fig 1.2: A map of the major CNS neurotransmitters grouped by chemistry, with the region or pathway and function of each.

Glutamate: the chief excitatory transmitter

Glutamate is the principal excitatory transmitter of the CNS, used at most fast excitatory synapses (cortex, hippocampus, spinal cord), acting on ionotropic and metabotropic receptors.

- **AMPA receptors** mediate fast excitation by gating Na^+ : the ordinary excitatory signal.
- **NMDA receptors** gate Ca^{2+} , but only when the cell is already depolarised, because Mg^{2+} blocks the pore at rest. This voltage dependence makes them central to synaptic plasticity, learning and memory.
- **Kainate receptors** are a further ionotropic class with modulatory pre- and postsynaptic roles.
- **Metabotropic glutamate receptors** adjust excitability more slowly through G-proteins.

Excitotoxicity is the pathological face: excessive glutamate release (stroke, head injury) over-activates NMDA receptors and floods the neuron with Ca^{2+} , triggering enzymatic self-destruction and cell death. This links glutamate to ischaemic neuronal loss and underlies the NMDA-channel blocker memantine in dementia.

GABA: the chief inhibitory transmitter

Gamma-aminobutyric acid (GABA) is the principal inhibitory transmitter of the brain, synthesised from glutamate by glutamic acid decarboxylase (GAD): the main excitatory transmitter is the precursor of the main inhibitory one. It acts on two receptor classes:

- **GABA-A receptor:** an ionotropic Cl^- channel; GABA opens it, Cl^- enters, the neuron hyperpolarises. Distinct allosteric sites: benzodiazepines raise the frequency of channel opening, barbiturates prolong its duration; both enhance GABA action and are sedative, anxiolytic and anticonvulsant.
- **GABA-B receptor:** metabotropic, opening K^+ channels and inhibiting Ca^{2+} channels for slow, prolonged inhibition. The muscle relaxant baclofen is a GABA-B agonist.

GABA is the brain's brake: loss of GABAergic inhibition produces seizures and anxiety, whereas enhancing it calms and anaesthetises.

Glycine: inhibition in the cord and brainstem

Glycine is the chief inhibitory transmitter of the spinal cord and brainstem. Like GABA-A, its receptor is an ionotropic Cl^- channel that hyperpolarises the neuron.

- **Strychnine** blocks the glycine receptor; removing glycinergic inhibition releases motor neurons, producing the violent spasms and convulsions of strychnine poisoning. Tetanus toxin causes similar rigidity by blocking glycine release.

Dopamine: four pathways, four clinical stories

Dopamine acts only through metabotropic receptors, in two families:

- **D1-like (D1, D5)** are excitatory, stimulating adenylyl cyclase.
- **D2-like (D2, D3, D4)** are inhibitory, inhibiting adenylyl cyclase. Most antipsychotic action is D2 blockade.

Four pathways, each with a distinct clinical effect:

1. **Nigrostriatal** (substantia nigra to striatum): coordinated movement. Degeneration causes Parkinson's disease; antipsychotic blockade causes drug-induced parkinsonism.
2. **Mesolimbic** (ventral tegmental area to limbic system): emotion, reward and the positive symptoms of schizophrenia; its overactivity is the target of antipsychotics.
3. **Mesocortical** (ventral tegmental area to prefrontal cortex): cognition and motivation; underactivity is linked to the negative symptoms of schizophrenia.
4. **Tuberoinfundibular** (hypothalamus to pituitary): dopamine tonically inhibits prolactin release, so D2 blockade raises prolactin and can cause galactorrhoea.

Serotonin (5-HT): mood and sleep

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine synthesised from tryptophan, with cell bodies in the raphe nuclei projecting across the whole brain. Through a large family of mostly metabotropic receptors (5-HT₃ is the ionotropic exception), it regulates mood, sleep and wakefulness, appetite and pain. Deficient serotonergic transmission underlies depression and anxiety, hence selective serotonin reuptake inhibitors raise synaptic 5-HT.

Noradrenaline, acetylcholine and histamine

- **Noradrenaline** arises from the locus coeruleus and acts on α - and β -adrenoceptors, governing arousal, the sleep-wake cycle and mood; deficiency contributes to depression alongside serotonin.
- **Acetylcholine** acts on nicotinic and muscarinic receptors and is central to learning and memory. Loss of basal-forebrain cholinergic neurons underlies the memory deficit of Alzheimer's disease, the rationale for cholinesterase inhibitors.
- **Histamine**, from hypothalamic neurons, acts on H1 receptors to maintain wakefulness. Central H1 blockade by first-generation antihistamines causes the familiar sedation.

Table 1.1: Excitatory versus inhibitory central transmitters

Feature	Excitatory transmission	Inhibitory transmission
Chief transmitter	Glutamate	GABA (brain); glycine (cord, brainstem)
Main receptor	NMDA, AMPA, kainate (ionotropic)	GABA-A, glycine (ionotropic Cl ⁻); GABA-B (metabotropic)
Ion movement	Na ⁺ / Ca ²⁺ influx	Cl ⁻ influx; K ⁺ efflux
Effect on membrane	Depolarisation (EPSP)	Hyperpolarisation (IPSP)
Net effect on neuron	Moves toward firing threshold	Moves away from threshold
Pathological excess	Excitotoxicity, seizures, stroke injury	Excess sedation, coma

The transmitter-to-disorder map

When a transmitter's signalling fails it produces a recognisable CNS disorder, and the drug class that treats it restores the signal. Table 1.2 is that map, to which every later chapter returns.

Table 1.2: Central transmitters and their linked disorders

Transmitter	Change in disease	Linked disorder	Therapeutic direction
Dopamine	Deficiency (nigrostriatal)	Parkinson's disease	Restore dopamine (levodopa)
Dopamine	Excess (mesolimbic)	Schizophrenia	Block D2 receptors (antipsychotics)
GABA	Reduced inhibition	Epilepsy, anxiety	Enhance GABA (benzodiazepines)
Serotonin / noradrenaline	Deficiency	Depression	Raise synaptic amine (SSRIs, TCAs)
Acetylcholine	Neuronal loss	Alzheimer's disease	Inhibit cholinesterase (donepezil)