SPMM Smart Revise

Pharmacodynamics

Paper A **Syllabic content 4.3**

1. Introduction

The term pharmacodynamics refers to the study of the mechanism of action of drugs (the effect of drugs on the body). Most psychotropics affect neurotransmitters of the brain. This effect can occur at various levels.

Level of action in neurotransmission cycle	Examples
Synthesis	L-tryptophan, l-dopa
Storage	Reserpine depletes NA and DA.
Release from storage	Amphetamine stimulates release of NA and DA
Reuptake	SSRI, TCA, cocaine – dopamine reuptake, Bupropion – dopamine & Noradrenaline reuptake
Degradation	MAO inhibitors, Acetyl cholinesterase inhibitors e.g. donepezil
Pre synaptic receptors	Clonidine, lofexidine at alpha2.
Post synaptic receptors	Most antipsychotics at D2
Partial agonism	Aripiprazole – D2; Buspirone 5HT1A; Clonazepam – BDZ receptor; Buprenorphine – opioid receptor mu
Antagonism	Flumazenil for benzodiazepines, antipsychotics at D2
Full agonism	Benzodiazepines at GABA-A complex, bromocriptine for dopamine
Second messengers	Lithium at inositol level.

Refer to Neurochemistry SPMM Notes for more details of different neurotransmitters, their structure and receptor actions.

2. Receptor mechanisms

The '**receptor'** of a drug can be defined generally as the cellular component to which the drug binds and through which the drug initiates the pharmacodynamic effects on the body. There are 2 major superfamilies; Ionotropic or metabotropic receptors.

- ***Ionotropic***: Theses are ligand-gated ionic channels. Their activation leads to a rapid transient increase in membrane permeability to either positive cations like sodium or calcium or negative anions like chloride. It causes excitation or inhibition of the postsynaptic membrane. Examples are nicotinic acetylcholine receptors, GABA-A receptors, glutamate receptors and serotonin 5HT 3.
- ***Metabotropic***: These produce slower response involving so-called G-proteins which bind to the intracellular portion of the receptor and activate a second messenger. Altered second messenger levels result in changes in the phosphorylation state of key proteins rendering them active or inactive. Examples are Dopamine (D1-5), Noradrenaline, and Serotonin 5HT1-7 except 5-HT 3, muscarinic acetylcholine receptors and opioid receptors (mu). Ionotropic receptors result in quick response ($GABA_{A,\,a}$ benzodiazepine); G protein coupling (metabotropic) is a comparatively slower process (most antipsychotics, antidepressants.

Kinetics of receptor binding: A drug can be an **agonist** for a receptor and can stimulate the biological activity of the receptor or could be an **antagonist** that inhibits the biological activity.

- **Full agonists** produce a maximal response. The measure of the degree of response is usually measured against physiological neurotransmitter efficiency for any given receptor.
- **Partial agonists** cannot elicit a maximal response and are less effective than full agonists. Examples are Aripiprazole, buspirone and buprenorphine. Partial agonists have a **ceiling effect**. The degree of response of a partial agonist depends on availability of physiological neurotransmitter in the vicinity; i.e. when maximal dopamine is available, partial agonist aripiprazole can actually inhibit the dopaminergic transmission as a less efficient molecule competes with more efficient molecule. In dopamine deficient states, the same partial agonist can enhance dopaminergic effects.
- An **inverse agonist** is an agent that binds to the same receptor but produces the opposite pharmacological effect. No clinical drug acts via this mechanism but several have been researched especially at GABA complex.
- **Antagonists** are drugs that interact with receptors to interfere with their activation by neurotransmitter or other agonistic molecules.

Types of antagonism

- **Competitive antagonism** can be reversed completely by increasing the dose of the agonist drug. Competitive antagonists reduce the potency (minimal dose needed to produce an effect) but not the efficacy (maximal response produced) of agonists. Examples of competitive antagonism include atropine at muscarinic receptors and propranolol at beta-adrenergic receptors.
- **Noncompetitive** antagonists alter the receptor site in some way so increasing the dose of the agonist drug can reverse the effects only partially. Non-competitive antagonism reduces both the potency and the efficacy of agonists. Therefore, non-competitive antagonists not only shift the curve to the right but also reduce the maximum effect. For example, ketamine and phencyclidine are noncompetitive NMDA antagonists. **Irreversible** antagonists bind irreversibly to the target site e.g. most traditional MAOIs.
- **Pharmacological antagonism** refers to the opposing action of two molecules by acting via same receptors. **Physiological antagonism** refers to the opposing action of two molecules by acting via different receptors e.g. acetylcholine vs. adrenergic actions.
- **Chemical antagonism** refers to the opposing action of two molecules by acting via chemical reactions. This is not seen in psychotropics, but heparin and protamine reaction is an example.

Most drugs bind reversibly to receptors, and the response is proportional to the fraction of receptors occupied (**law of mass action**). As the concentration of drug increases, the responses increases until all receptors are occupied giving a dose-response curve.

Receptors can be up-regulated or down-regulated by drugs. With therapeutic use, agonists may cause **down-regulation** (desensitivity) or reduction in receptor numbers while antagonists may have the opposite effect- **upregulation** (hypersensitivity) or increase in receptor numbers.

The potency of a drug with receptor binding action refers to the amount of the drug needed to produce a particular effect compared to another standard drug with similar receptor profile ('vigor'). The potency of a drug is determined by;

a. The proportion of the drug reaching the receptor
b. The affinity for the receptor
c. Efficacy

Affinity refers to the ability of the drug to bind to its appropriate receptor ('affection'). Drugs that bind readily to a receptor are described as having high affinity for that receptor and, in general, the higher the affinity and the more receptor a drug occupies, the more potent it is.

Efficacy refers to how well the drug produces the expected response i.e. the maximum clinical response produced by a drug ('productivity'). Efficacy depends on affinity, potency, duration of receptor action in some cases and kinetic properties such as half-life, among other factors.

Haloperidol is more potent than chlorpromazine as approximately 5 mg of haloperidol is required to achieve the same effect as 100 mg of chlorpromazine. These drugs, however, are comparable in the maximal clinical response achievable using them i.e. equally efficacious but not equipotent.

3. Modes of therapeutic action for psychotropics

Antipsychotic drugs

In general all antipsychotics act via varying degrees of D2 blockade. Aypical drugs show selectivity for D2 receptors and also show high 5HT2: D2 blocking ratio. Specific actions are listed below.

DRUG	MECHANISM
Amisulpride	Both D2 and D3 antagonism. Similar dose-dependent pre & postsynaptic profile to sulpride. Some degree of limbic selectivity and 5HT7 activity also noted.
Aripiprazole	Partial dopamine agonist at D2. Also 5HT2A antagonist. Exhibits a **Goldilocks' phenomenon** -stabilising action wherein anatagonising DA at sites of excessive dopamine such as mesolimbic zones while mimicking DA (agonism) at dopamine deficient zones such as mesocortical areas that are linked negative symptoms. Does not produce much change in tuberoinfundibulum where normal DA levels are expected in schizophrenia. Aripiprazole acts on both postsynaptic D_2 receptors and presynaptic autoreceptors.
Asenapine	D2 antagonist and serotonin 5HT2A blocker (similar to olanzapine). Has potent alpha-2 blockade effect. Sublingual; allegedly weight and prolactin-neutral. Licensed for use in mania.
Chlorpromazine, promazine	The moderate antimuscarinic effect in addition to D2 blockade. Highly sedative phenothiazine drugs.
Clozapine	A High ratio of 5HT2 to D2 blockade; also blocks D4 and 5HT6 receptors. Has notable alpha 1 antagonism and anticholinergic and antihistaminic properties. Weak D1 and D2 affinity. Also binds 5HT3. Proposed to have a faster dissociation rate (similar to quetiapine) hence a hit and run profile is noted.
Lurasidone	D2 antagonist and serotonin 5HT2A blocker (similar to risperidone). Also has a high affinity for serotonin 5HT7; partial agonist at 5HT1A receptors. Has minimal affinity for alpha-1 (less orthostatic effect) and histamine receptors (thus may be weight neutral)
Olanzapine	Atypical antipsychotic. Has high 5HT2 / D2 blockade ratio. Potent D4 blockade and 5HT6 blockade also noted. It has significant anticholinergic and some antihistaminic effects.
Paliperidone	A metabolite of risperidone. Similar mechanism of action
Quetiapine	Similar to clozapine – hit and run profile on D2. Compared to other atypicals it has somewhat lesser 5HT2A blockade. Significant anticholinergic effects similar to olanzapine.
Risperidone	Serotonin-Dopamine Antagonist - Atypical Antipsychotic. Has high 5HT2A antagonistic property. In higher therapeutic doses can bind to D2 in a similar fashion to typicals and can lead to extrapyramidal and prolactin related side effects.
Sulpiride	Pure D2 antagonist. At low doses presynaptic receptors blocked (helps negative symptoms?); above 800mg/day doses, affects postsynaptic D2 – reducing positive symptoms.
Thioridazine, pericyazine,	D2 antagonists. Marked antimuscarinic effect. Less EPSEs than other typicals.

pipotiazine	
Thioxanthenes	Exhibit stereoisomerism. D2 antagonists – typical antipsychotics.
Ziprasidone	Atypical antipsychotic with 5-HT_{2A} and D_2 blockade. Antagonizes 5-HT_{1D}, 5-HT_{2C}, D_3, D_4 receptors. Poor affinity for muscarinic effects; some antihistaminic property noted. Agonistic at 5-HT_{1A}; also some serotonin and norepinephrine reuptake inhibition noted.
Zotepine	Atypical antipsychotic with 5HT2A, 5HT2C, D1, D2, D3, D4 antagonism. Potent noradrenaline reuptake inhibitor. Potent antihistaminic activity and some NMDA antagonism.

Antidepressant drugs

DRUG	MECHANISM
Agomelatine	Agomelatine enhances norepinephrine and dopamine neurotransmission through 5-HT2C antagonism. It is also a direct agonist at melatonin (MT1 and MT2) receptors. GABA interneurons tonically inhibit noradrenergic circuits (from locus coeruleus) and dopaminergic circuits (from ventral tegmentum) projecting to the prefrontal cortex. Serotonin via 5HT2C stimulation drives these GABA interneurons. Thus, norepinephrine and dopamine circuits are inhibited by the normal tonic release of serotonin onto 5-HT2C receptors (Stahl, 2007). Thus agomelatine, through 5HT2C inhibition, acts as norepinephrine and dopamine disinhibitor (NDDI). Antidepressant with possible sedative effects.
Amoxapine	Tetracyclic with dibenzoxazepine structure. Has both dopamine antagonistic and serotonin-noradrenaline reuptake inhibition effects. So claimed to have significant antipsychotic properties in addition to antidepressant effects. Similarly, extrapyramidal side effects are seen more often than other tricyclic.
Bupropion	Dopamine and noradrenaline reuptake inhibitor. Used to help quit smoking and in depression. It is noted to increase the efficiency of noradrenergic transmission and reduce total norepinephrine turnover. It has no antimuscarinic activity. Some degree of competitive nicotinic antagonism.
Buspirone	Partial agonist on serotonin 5-HT_{1A} receptors. At presynaptic levels, it is mostly a full agonist, which inhibits the release of serotonin, with consequent antianxiety effects. Partial agonist action at postsynaptic receptors appears to account for the antidepressant activity.
Citalopram	SSRI, most selective of all SSRIs for serotonin reuptake. Occurs in a racemic mixture of which s isomer has pharmacological activity. But r- enantiomer inhibits the action of s- enantiomer; hence if escitalopram is used (s- enantiomer) lesser dose is sufficient.
Clomipramine	Tricyclic – regarded as most potent; higher SRI selectivity than other TCAs but lesser selectivity than SSRIs.
Desipramine	Tricyclic with least anticholinergic action but lethal on overdose.
Duloxetine	SNRI similar to venlafaxine. Said to have a better profile for psychosomatic pain and neuropathic pain.
Levothyroxine & Liothyronine	Levothyroxine is T4; liothyronine is T3 – both are thyroid hormones; suppress TSH and acts as an adjuvant in resistant depression. The exact mechanism of antidepressant effects unknown – possibly via neuroendocrine changes.
Lithium	Lithium is thought to act via the second messenger system. It putatively enhances serotonin transmission by 1. Increasing tryptophan uptake into neurons 2. Enhancing serotonin release 3. Downregulation of 5HT1A, 1B and 2 receptor subtypes is also noted on chronic administration. 4. Directly inhibiting glycogen synthase kinase-3 (GSK-3) and also 5. Competing with magnesium directly at several important regulatory enzymes such as inositol-monophosphatase (IMPase), which catalyzes inositol second messenger system.

	According to the inositol depletion hypothesis, inhibition of IMPase by lithium reduces myoinositol and phosphoinositide phosphate (PIP-2), leading to therapeutic efficacy. Further, through an increase in intracellular sodium, it may also affect Na+K+ pump and reducing dopamine synthesis in dose-dependent fashion.
Milnacipran	SNRI similar to venlafaxine. New drug Levomilnacipran also acts similarly
Mirtazapine	5HT2A antagonism, alpha 2 antagonism, anti histaminic and anti 5HT3 properties noted. Mianserin has similar profile, but it is not antihistaminic; instead it has anticholinergic properties.
Moclobemide	Reversible inhibitor of MAO-A selectively.
Nefazadone	5HT2 antagonist with some serotonin reuptake inhibition and mild norepinephrine reuptake inhibition. Has some alpha 1 antagonistic effect. Produces mCPP as a metabolite.
Paroxetine	Selective Serotonin Reuptake Inhibitor – most potent of all SSRIs in serotonin reuptake blockade, but not specific – has significant antimuscarinic action.
Phenelzine	Monoamine Oxidase Inhibitor – increased availability of monoamines including serotonin and noradrenaline may explain the mechanism of antidepressant action though disputed.
Pindolol	Beta blocker with intrinsic sympathomimetic activity. Also 5HT1A antagonism – tipped to enhance the onset of action of SSRIs through this mechanism.
Reboxetine	Noradrenergic specific reuptake inhibitor (NARI)
Selegiline	Monoamine Oxidase Inhibitors – selective for B at normal therapeutic doses; selectivity lost when a patch is applied at higher doses, leading to some antidepressant action.
SSRIs	Reuptake inhibition at somatodendritic areas takes place soon after administration – this leads to down regulation of somatic autoreceptors for serotonin and as a consequence inhibitory tone on serotonergic transmission is lost; the serotonergic output is facilitated. (see below)
Tranylcypromine	Monoamine Oxidase Inhibitors. Irreversible, non-selective. Positive enantiomer better MAOI, negative enantiomer better reuptake inhibitor.
Trazodone	5HT2A/2c antagonism and some alpha 2 blockade. Alpha 1 blockade and antihistaminic properties also noted. Feeble reuptake inhibition at serotonin transporters.
Tricyclics	Monoamine reuptake inhibition (see below). The varying degree of noradrenaline and serotonin reuptake inhibition. Very minimal negligible effect on dopamine. Clomipramine is the most serotonin specific. Secondary amines are more noradrenergic.
Venlafaxine	SNRI. Serotonin noradrenaline reuptake inhibitor. Acts as an SSRI in lower (<150mg) doses.
Vilazodone	Mechanism not fully understood but selective serotonin reuptake inhibition and also a partial agonist action at serotonergic 5-HT1A receptors (the chemical structure is close to trazodone and nefazodone)
Vortioxetine	A structure similar to reboxetine but predominantly an SSRI-like effect. In addition, also shows 5HT3 antagonism and 5HT-1A agonism.

Selectivity of antidepressants: The ratio of concentration required to produce equivalent inhibitions of serotonin (5-HT) to Noradrenalin is shown below.

- Amitriptyline 1:1
- Clomipramine 1:7
- Fluoxetine 150:1
- Citalopram >2000:1

Inhibition of nerve terminal NE neuronal uptake system

↓

Increase in synaptic concentrations of NE

↓

Desensitization of inhibitory Alpha2-adrenoceptors in the terminal

↓

Increase in neuronal NE release

↓

Further increase in synaptic concentrations of NE

↓

Desensitization of postsynaptic Beta adrenoceptors without affecting postsynaptic Alpha1-adrenoceptor sensitivity

Mechanism of TCA Action

5HT Reuptake inhibition at somatodendritic areas

↓

Increase in local concentrations of 5HT

↓

Desensitisation of inhibitory 5HT1A autoreceptors in the soma

↓

Increase in neuronal 5HT release

↓

Increase in synaptic concentrations of 5HT

↓

Desensitization of presynaptic 5HT1B receptors without affecting postsynaptic 5HT1A sensitivity

Mechanism of SSRI Action

Mood stabilizers

DRUG	MECHANISM
Carbamazepine	Prolongs sodium channel inactivation. As a consequence, calcium channel inactivation is prolonged. It also reduces glutamate neurotransmission, adenosine A1 receptor antagonism and increase in brain catecholamine activity. It inhibits peripheral benzodiazepine receptors and reduces limbic kindling. It interferes with glial cell steroidogenesis.
GABApentin	GABA analogue structurally - binds to the $\alpha 2\delta$ subunit of the voltage-dependent calcium channel in the central nervous system. Acts on l-amino acid transport and thus can increase GABA availability in the brain. It crosses BBB via this l-AA transport. Has a high-affinity site in GABA-A complex; but no benzodiazepine-like actions noted.
Lamotrigine	Blockade of voltage-sensitive sodium channels leading to modulation of glutamate and aspartate release; some effect on calcium channels. Some inhibition of serotonin reuptake and weak inhibition of 5-HT_3 receptors.
Levetiracetam	Indirectly enhance GABA system. Anticonvulsant with weak evidence against mania.
Oxcarbazepine	A metabolite of carbamazepine; similar mechanisms proposed.
Pregabalin	GABA analogue structurally (similar to gabapentin). Like gabapentin, pregabalin binds to the $\alpha 2\delta$ subunit of the voltage-dependent calcium channel in the central nervous system. This may subtly reduce the release of certain neurotransmitters. It may as well influence GABergic neurotransmission. It has anti-epileptic, analgesic (neuropathic pain) and anxiolytic effects. It is more potent than gabapentin hence has a higher therapeutic index and fewer dose-related side effects.
Tiagabine	Tiagabine is a potent and selective reuptake inhibitor of GABA. It also has mild antihistaminic effects.
Topiramate	Topiramate is a fructose derivative; it is a selective inhibitor of Glutamate AMPA receptors, blocks Na^+ receptors, and has indirect GABAergic activity by potentiating the action of $GABA_A$ receptor.
Valproic acid	Unknown- speculated to act via increased GABA release, decreased GABA metabolism, increased neuronal responsiveness to GABA and increased GABA receptor density, inhibition of phosphokinase C similar to lithium and functional dopamine antagonism.
Vigabatrin	VIGABATRIN expands as Vi- GABA- TR-transaminase IN- inhibitor. The name explains the mode of action.

Sedatives & Hypnotics

DRUG	MECHANISM
Benzodiazepines	Act via a particular site called omega site in GABA-A complex. All are agonists except clonazepam, which is a partial agonist. They facilitate GABA action on GABA-A complex – thus facilitating inhibitory neurotransmission via chloride ions. They have no direct agonistic action in the absence of GABA. They do not increase the number but the frequency and duration of chloride channel opening.
Chloral hydrate, paraldehyde and meprobamate	Barbiturate like agents. Probably potentiate GABAergic neurotransmission. Paraldehyde is cyclic ether. They have a poor safety profile and hence none of these are in clinical use currently.
Flumazenil	Benzodiazepine antagonist
Ramelteon	Ramelteon is a melatonin receptor full agonist with high affinity and selectivity for human melatonin receptors MT1 and MT2 over the MT3 receptor. It decreases sleep latency and increases sleep time across all ages; the dose-response curve is flat with no significant difference in efficacy between the 16-mg or 64-mg doses of ramelteon. It may have lower abuse potential than other hypnotics
Thiopental	Act directly on GABA-A complex and facilitate GABA transmission by opening chloride channels and enhancing hyperpolarisation. At lower doses, barbiturates enhance GABA by decreasing the rate of GABA dissociation and increasing the duration (not a number) of GABA-activated chloride channel opening. At slightly higher concentrations, barbiturates directly activate chloride channel opening even in the absence of GABA, an action that is not shared by benzodiazepines.
Zolpidem, Zaleplon, Zopiclone, eszopiclone	Z-drugs act via GABA A complex but act differently than benzodiazepines. Benzodiazepines occupy all 3 subunits of the ω receptor, but Z-drugs occupy only certain subunits. e.g,. zolpidem and zopiclone acts on ω1 receptors – hence no muscle relaxant, anxiolytic and anticonvulsant effects noted. Also, slow wave sleep is unaffected. Zaleplon occupies all 3 ω receptors. Zopiclone occurs as a racemic mixture where only s-isomer is active (eszopiclone).

Z HYPNOTICS

Given their selectivity on BDZ-receptor subunits, Z-drugs are less likely to impact sleep stages and have a lower risk of tolerance and dependence compared with benzodiazepine hypnotics

Zopiclone is the least selective of all Z-drugs

Addiction pharmacology

DRUG	MECHANISM
Alcohol	Intercalates into the fluid cell membrane; decreases NMDA sensitivity; increases GABA sensitivity; down-regulates calcium channels; up-regulates nicotine receptor gated sodium channels.
Amphetamine	Acts via releasing stored monoamines especially noradrenaline and dopamine. Hence a central sympathomimetic.
Buprenorphine	Partial opioid agonist. Lower doses – mild agonism; higher doses – antagonistic effects.
Cannabis	Acts via cannabinoid receptors. CB1 is central and activated by 11OH tetra hydro cannabinoid. This inhibits GABA tone in the substantia nigra and other areas. May be related to increased dopamine activity at reward centres. CB2 is peripheral immune-related and seen in spleen and thymus. (Endogenous cannabinoids called anandamides are derived from arachidonic acid; their function is unclear)
Clonidine, lofexidine	Presynaptic alpha 2 agonist – reduces central sympathetic tone. Opioid receptors on locus coeruleus projections reduce noradrenergic tone on long-term use. The cellular machinery compensates via up-regulation of adenylate cyclase and maintains sympathetic tone in a chronic user. Sudden withdrawal leads to increased adrenergic firing rate (withdrawal symptoms); hence alpha 2 autoreceptor stimulation which reduces central sympathetic tone helps in opioid withdrawal.
Dexfenfluramine & Fenfluramine	Produce massive serotonin release from nerve endings. [Fen-Phen was an off-label combination of fenfluramine and phentermine used for promoting weight loss but fenfluramine (and dexfenfluramine) was withdrawn due to irreversible serotonergic damage, valvular regurgitation and pulmonary fibrosis].
Disulfiram	Inhibits aldehyde dehydrogenase. Leads to accumulation of acetaldehyde if alcohol is consumed producing unpleasant reactions.
Levomethadyl acetate (LAAM)	Long-acting opioid agonist; potentially similar use as methadone. Withdrawn due to prolonged QT and torsades de pointes. Pure mu agonist.
LSD	5HT2A partial agonism producing hallucinogenic effect
MDMA	Has 2 isomers → R(-) isomers produce LSD-like effects and the S(+) isomers have amphetamine-like properties LSD-like action is mediated via serotonin release from presynaptic neurons. In the long term, this can damage serotonergic tracts irreversibly.
Methadone	Opioid receptor agonist. Longer acting than heroin and orally available. Pure mu agonist.
Naloxone	Short-acting opioid mu antagonist
Naltrexone	Longer acting opioid mu antagonist
Phencyclidine	Noncompetitive NMDA antagonist similar to ketamine; also binds to sigma receptors
Varenicline	Varenicline (Champix) is a partial agonist at the $\alpha 4\beta 2$ unit of nicotinic acetylcholine receptor. It assists smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine.

Anti dementia drugs

DRUG	MECHANISM
Donepezil, Galantamine, Rivastigmine	Cholinesterase Inhibitors. The act by inhibiting acetyl cholinesterase enzyme that breaks down acetylcholine centrally. Rivastigmine inhibits both the acetyl and butyl-cholinesterase while donepezil and galantamine are acetyl specific. Galantamine also has nicotine agonistic properties.
Memantine	Blockade of N-methyl-d-aspartate (NMDA) glutamate receptors. Unlike ketamine, which is a high-affinity noncompetitive blocker, memantine is a non-competitive blocker with low affinity and binds only to actively open NMDA channels. Its receptor dissociation rate is relatively fast, and so it does not accumulate and interfere with normal NMDA activity.

- Acetylcholine is inactivated by both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Cholinesterase inhibitors increase the amount of ACh available through inhibition of these enzymes.
- An acetylcholinesterase inhibitor can work at either of two sites on AChE, an ionic subsite or a catalytic esteratic subsite; Tacrine and donepezil act at the ionic while physostigmine and rivastigmine act at the catalytic esteratic subsite.
- Tacrine, and to some extent rivastigmine are non-selective inhibitors of both AChE and BChE.
- CNS specific inhibition of AChE can occur with donepezil.
- Binding to the AChE sites may be either reversible or irreversible, and may be competitive or noncompetitive with acetylcholine.
- Galantamine is a competitive drug while tacrine is a non-competitive inhibitor.
- AChE tetramer, G4, is located on the presynaptic membranes while a monomer, G1, is found on postsynaptic membranes. Although G4 is decreased along with the neuronal loss in AD, postsynaptic cholinergic receptor neurons and G1 ACh are not decreased significantly with AD or aging. Rivastigmine and to some extent galantamine are highly selective for the postsynaptic G1 monomer while donepezil is not selective.

RILUZOLE

It is approved for use in Motor Neuron Disorder. It is unclear whether this would help features of fronto-temporal dementia associated with MND. It prolongs survival by nearly 10% for more than a year of treatment.

Riluzole's mechanism of action is via 1. Sodium channel blockade 2. High-voltage calcium channel blockade 3. NMDA-glutamate receptor antagonism.

It preferentially blocks the sodium channels in damaged neurons, reducing calcium flow and indirectly preventing excitotoxic damage.

Miscellaneous drugs

DRUG	MECHANISM
Amantadine	Used in Parkinsonism. It augments dopaminergic neurotransmission through an unknown mechanism.
Dextroamphetamine Methylphenidate	Methylphenidate, dextroamphetamine, and amphetamine are indirectly acting sympathomimetics – induce the release of dopamine and Noradrenaline from presynaptic neurons. Dextroamphetamine and methylphenidate are also weak inhibitors of catecholamine reuptake and inhibitors of monoamine oxidase.
Atomoxetine	Tricyclic like structure – phenylpropanolamine derivative. Selective inhibitor of the presynaptic noradrenaline reuptake (NARI) similar to the antidepressant reboxetine.
Benztropine, Biperiden, Orphenadrine, Procyclidine	Anticholinergic drugs. Used in the treatment of EPSEs induced by antipsychotics.
Carbidopa	Carbidopa inhibits aromatic-L-amino-acid decarboxylase (DOPA Decarboxylase). Administered together with l-dopa as Sinemet to reduce the peripheral conversion of dopa to dopamine. Carbidopa cannot cross the blood-brain barrier.
Dantrolene	Directly affects the formation of actin-myosin complexes in skeletal muscle through ryanodine calcium channel inhibition.
Diphenhydramine, Hydroxyzine, Promethazine, Cyproheptadine.	Antihistaminic drugs against central histamine H1 receptor. Cyproheptadine has both a potent antihistamine and serotonin 5-HT_2 receptor antagonist properties. All of these agents have some antimuscarinic properties too. Cyproheptadine was used as anti-anorexic agent, and also to treat delayed ejaculation associated with SSRI use.
Levodopa	Dopamine precursor used in parkinsonism; is combined with carbidopa to reduce peripheral conversion to dopamine.
Modafinil	Activates hypocretin-producing neurons possibly through alpha 2 and/or alpha-1 adrenergic agonist properties (alerting effects) or some noradrenaline reuptake blocking effects; the stimulating effect of modafinil can be attenuated by prazosin.
Pemoline	Indirectly stimulates dopaminergic activity - but it has little actual sympathomimetic activity. A stimulant. Withdrawn due to hepatotoxicity.
Reserpine	Depletes the stored dopamine and other monoamines from vesicles. Can lead to depression and suicide.
Sildenafil	Phosphodiesterase-5 Inhibitor.
Propranolol .	Beta-adrenergic antagonist. Lipophilic and so can pass blood brain barrier and can have central actions. Reduces akathisia and peripheral signs of sympathetic overdrive seen in anxiety
Pramipexole, ropinirole, apomorphine	Apomorphine, pramipexole, and ropinirole are dopamine agonists - bind about 20 times more selectively to dopamine D_3 than D_2 receptors. Bromocriptine is less selective 2:1. Pergolide is most selective 5:1. Bromocriptine and pergolide are ergotamine derivatives. Pramipexole is a nonergot dopamine agonist. Apomorphine is structurally related to morphine and other opioids.
Sumatriptan	5HT1D and 1F agonist
Yohimbine	It is an alpha 2 antagonist sometimes used in treating erectile dysfunction.

Lorcaserin, phentermine-topiramate combination, and naltrexone-bupropion combination are novel FDA approved treatment approaches to tackle obesity. These drugs are promoted as anorectic agents, similar to fenfluramine-phentermine combination ('fen-phen'), rimonabant, and sibutramine (all of the latter 3 which fell out of favour due to various adverse effects). Lorcaserin is a serotonin 2C receptor agonist; it is prescribed twice daily with an instruction to discontinue if 5% weight loss is not achieved by 12 weeks. The commonest side effect is a headache. In diabetic patients, this drug can induce hypoglycaemia.

Phentermine is a sympathomimetic amine while **topiramate** is an antiepileptic drug. This combination is used in an extended-release preparation. Side effects include paraesthesia, dysgeusia and dizziness. **Naltrexone** is an opioid antagonist while **bupropion** is an aminoketone antidepressant that promotes weight loss in subjects even as a standalone drug (so a prescription of bupropion is not advised in those with a history of eating disorders).

4. Neurochemical effects of ECT

- Repeated subconvulsive electrical stimulation in animals reduces the seizure threshold – this process is called kindling. ECT does NOT produce a kindling effect; in fact it protects against kindling in animal studies. Thus, it can be termed an **anti-kindling agent**. As a result, dosing may need to be increased over the course of treatment to achieve the same seizure-inducing effect.
- Hippocampal neuronal loss occurs in kindling. But ECT results in neurogenesis in the rat. This could be mediated by an increased expression of brain-derived neurotrophic factor and its receptor,
- **Blood–brain barrier permeability** acutely increases following ECT but returns to baseline within 24 hours
- Imaging studies show that ECT is not associated with markers of cell loss or damage e.g. there is no change in myelin basic protein immunoreactivity or neuron-specific enolase in serum. Tau protein, neurofilament and S-100 beta protein, markers of neuronal and glial damage, are also unchanged after ECT.
- EEG shows delta and theta activity after applying ECT. This pattern returns to normal after 3 months of the end of treatment.

Variables affected by ECT	Changes
Neurotrophic factors	Increase in NGF,BDNF, NF3.
Cell growth and synaptic connectivity	Increased esp. In hippocampus
Hormones	Increased cortisol, prolactin, TSH coincides with good response. TRH gene expression increased in animals. Vasopressin, ACTH, oxytocin and opioid endorphins also increase consistently.
Neurotransmitters and their receptors	5-HT-, NA-, cholinergic-, glutaminergic- and GABAergic systems, adenosine A1-receptor & 5-HT2A – all decrease in sensitivity. Activation of DA transmission and stimulation of 5-HT in hippocampus and amygdala.

- An increase in $5HT_2$ receptors are noted in rodents after applying electrical stimulation; this change is opposite to the changes noted after administering antidepressant drugs. But note that using a [18F] setoperone PET scan Yatham et al. (2010) have now demonstrated that unlike in rodents, and similar to antidepressants, ECT reduces brain 5-HT2 receptors in individuals with depression.
- ECT also reduces β noradrenergic receptors and increases noradrenaline turnover. Further alpha 2 receptors are reduced after ECT, similar to antidepressants.

5. Psychopharmacogenetics

Psychopharmacogenetics focuses on how polymorphisms in genes affecting the mechanism of action of a drug's effect and/or metabolism (both peripheral and central) can influence an individual's clinical response to the drug, in terms of both therapeutic efficacy and adverse effects.

Drug	Effect	Biological substrate
Nicotine replacement	Response to nicotine replacement (esp. in women)	Dopamine receptor DRD2 variant
Clozapine	Drug response	No association with DRD2 variants DRD3 Ser9Gly polymorphism – controversial DRD4 polymorphisms– no correlation 5HT2A receptor polymorphism – associated 5HT2C receptor polymorphism – associated 5HT transporter linked polymorphic region (5HTTLPR) – associated CYP2D6 variations – overall efficacy not affected
Methylphenidate	Poor response of ADHD symptoms.	Homozygosity for the 10-repeat allele at *DAT1*
Clozapine	Agranulocytosis	HLA loci variants
Typical antipsychotics		No association with DRD2 variants DRD3 Ser9Gly polymorphism – associated DRD4 polymorphisms– no correlation 5HT2A receptor polymorphism - associated
Typical antipsychotics	Extrapyramidal symptoms, postural hypotension & excess sedation	Poor metabolizers of CYP2D6
Typical antipsychotics	Acute akathisia	Polymorphisms in *DRD3* and *DRD2*
Typical antipsychotics	Tardive dyskinesia	*DAT* polymorphism, *5-HTTLP*R and the tryptophan hydroxylase (*TPH*) polymorphism and to some extent CYP1A2 polymorphisms
Typical antipsychotics	Hyperprolactinaemia & NMS	*DRD2* polymorphism

The serotonin transporter (5-HTT) protein acts as the primary mechanism for removing 5-HT from the synaptic cleft. Two polymorphisms have been identified within the human *5-HTT*, an insertion/deletion polymorphism in the promoter region (5-HTTLPR) results in a short (*s*) and a long (*l*) variant, and a VNTR polymorphism in intron.

6. Ethnopharmacology

Ethnicity is defined as a self-ascribed belongingness to a group with common geographical origins, race, language, religion, etc., which transcends kinship and neighbourhood. Ethnic categories retain a strong racial component. **Race** on the other hand is largely perceived by appearance and attributed to biological and genetic traits. **Culture** is a shared system of concepts or mental representations established by convention and reproduced by traditional transmission.

Differences exist in the placebo response, compliance, doctor-patient relationship, social stress and health beliefs. The following are differences in the pharmacology of drugs administered.

Absorption and availability

- Caucasians appear to have lower plasma levels of tricyclic antidepressants and attain plasma peaks later when compared with Asians (of Far Eastern ancestry as well as those from the Indian subcontinent). These differences have been attributed to a greater incidence of **slow hydroxylation** among Asians when compared with Caucasians
- Maximal haloperidol concentration in plasma after rapid tranquillisation is significantly high for Asians than Caucasians (Lin & Finder, Am J Psychiatry 140:490-491, 1983).

Metabolism

- In the CYP system, variations in **CYP2D6** are largely determined by genetic factors. (CYP2D6 metabolizes a number of antidepressants, antipsychotics, beta-adrenoceptor blockers, and antiarrhythmic drugs). The CYP2D6 variation is called debrisoquine/sparteine polymorphism: 4 groups exist –
  1. **Poor metabolizers**: develop side effects quickly. Caucasians - the highest rate of poor metabolizers (nearly 7%). East Asians - lowest – 1%. These 7% Caucasians and 1% East Asians lack this enzyme, and so are poor metabolizers of risperidone and tricyclics
  2. **Intermediate metabolizers**: higher in Asians (most Asians fall into this group – hence have more side effects though good drug efficacy)
  3. **Extensive metabolizers**
  4. **Ultrarapid metabolizers**: need high doses. 33% North Africans have multiple copies of CYP2D6, and so are ultra-rapid metabolizers. They require higher doses of risperidone. Only 5% Caucasians and 1% East Asians are ultra-rapid. 25% Indians may have this variant.
- **CYP2C19** enzyme participates in the metabolism of omeprazole, propranolol and psychotropic drugs such as hexobarbital, diazepam, citalopram, imipramine, clomipramine, sertraline and amitriptyline. The incidence of poor metabolizers of CYP2C19 substrates is

much higher in Asians (15–30%) than in Caucasians (3–6%). CYP2C19 polymorphism is mephenytoin related.

- ✶ Unlike CYP2D6, the variations in **CYP3A4** often influenced by environmental (e.g. diet) factors.
- ✶ Nearly 40% Asians and around 60% South American Native Indians lack **Aldehyde dehydrogenase** enzyme in sufficient amounts to metabolise alcohol – this serves as a natural deterrent in these communities.

Pharmacodynamics

The long form serotonin transporter polymorphism in Caucasians is associated with better SSRI response and tolerance while the opposite is true in South East Asians. Low COMT variant is seen in less than 20% of Asians and Africans, but nearly 50% of Caucasians show low variant.

Adverse effects

- ✶ A well-known example from general medicine is that of Isoniazid – East Asians are most likely to be **rapid acetylators** and suffer from hepatotoxicity. But they have lesser peripheral neuropathy seen in slow acetylators.
- ✶ Chinese people had higher levels of extrapyramidal side-effects with haloperidol, and their blood levels were comparably high on equivalent dosages.
- ✶ On the administration of antipsychotics, Asian subjects were reported to produce greater serum prolactin levels than Caucasian subjects. This remains statistically significant after controlling for the difference in haloperidol concentrations, suggesting that the two groups differ in their dopamine receptor-mediated response.
- ✶ A summary of some relevant ethnic effects is given below.

African Americans	**Asians**
• Increased diagnosis of schizophrenia but decreased diagnosis of depression • Have more side effects with lithium, tricyclics • Higher tardive dyskinesia with antipsychotics. • Better, rapid response to tricyclics and lorazepam, but poor response to fluoxetine. • More depot medications received by African Americans.	• It is best to start at half of the standard dosage of all psychiatric medications • Clozapine better effect in lower serum range, but higher incidence of agranulocytosis • Taiwanese have lower required therapeutic level of lithium. • Metabolise TCA slowly. • Asians use herbal remedies more often than others.

Gender differences in psychopharmacology

- Antipsychotic response is shown to be superior in women
- In chronically ill population, men are found to require twice as high a dose as women for effective maintenance.
- Women have higher **antipsychotic plasma levels** than men after receiving the same dose of the drug.
- The enzyme **CYP1A2** appears to be less active in women than in men, leading to relatively higher blood concentrations of olanzapine and clozapine in women.
- The volume of distribution of **lipophilic** drugs, such as antipsychotics, is greater in women than in men
- In women, the blood volume is smaller, but **lipid compartments** are larger. This prolongs the half-life of antipsychotics in the body, leading to accumulation over time, a phenomenon that becomes important when administering **depot injections**. After a steady state is achieved, dosing intervals for women should be longer than for men.
- **Acute dystonia**, long thought to be more prevalent among men, has been shown now to be more frequent in females at equivalent doses. Earlier clinical studies had not taken into account the fact that young male patients were commonly given higher doses than women.
- **Pulmonary embolism** (a rare problem seen with drugs that have an affinity for the serotonin 5-HT_{2A} receptor) and **tardive dyskinesia** appear to be more common in women.

DISCLAIMER: This material is developed from various revision notes assembled while preparing for MRCPsych exams. The content is periodically updated with excerpts from various published sources including peer-reviewed journals, websites, patient information leaflets and books. These sources are cited and acknowledged wherever possible; due to the structure of this material, acknowledgements have not been possible for every passage/fact that is common knowledge in psychiatry. We do not check the accuracy of drug related information using external sources; no part of these notes should be used as prescribing information.

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