05 - Antidepressant drugs

Antidepressant drugs

© SPMM Course Antidepressant drugs DRUG MECHANISM Agomelatine Agomelatine enhances norepinephrine and dopamine neurotransmission through 5HT2C 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-HT1A 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.

© SPMM Course 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.

© SPMM Course 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

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 TCA Action Mechanism of SSRI Action

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