08 - Addiction pharmacology

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© SPMM Course 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combination of fenfluramine and phentermine used for promoting weight loss but fenfluramine (and dexfenfluramine) was withdrawn due to irreversible serotonergic damage, valvular regurgitation and pulmonary fibrosis].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 Withdrawn due to prolonged QT and torsades de pointes.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 α4β2 unit of nicotinic acetylcholine receptor. It assists smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine.

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