

# Pharmacology of drugs of abuse.

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# Overview of lecture.

- 1.New guidelines for classification of drugs of abuse.
- 2.What do drugs of abuse do?
- 3.Psychopharmacology of cannabis.
- 4.Psychopharmacology of alcohol.
- 5.Novel psychotropic drugs of abuse.
- 6.Is there a role for hallucinogens in psychiatry?
- 7.Treatment aspects.

# New Guidelines for Drugs of Abuse.

- British Association of Psychopharmacology Guidelines: evidence based for the pharmacological management of substance abuse, harmful use, addiction and comorbidity.
- Lingford-Hughes A.et al.  
J.Psychopharmacology,26 (7) 899-952,2012.

# Classification of drugs of abuse in U.K.[1971]

- CLASS A: Heroin, Cocaine, LSD, Ecstasy (MDMA), Psilocin, Methamphetamine.
- CLASS B: Amphetamine, Barbiturates, Codeine, Methylphenidate
- CLASS C: Cannabis, Benzodiazepines, Anabolic steroids, Ketamine, Gammahydroxybutyrate (GHB).
- Classification: confused, inconsistent and arbitrary!

# Classification of drugs of abuse as total harm scores-1.

- The current classification according to the Misuse of Drugs Act does not include alcohol or tobacco which are responsible for major health and social problems.
- An Independent Scientific Committee on Drugs was established by an expert group in the U.K. to revise the drug list to account for their harm to the individual, society and the economy.

# Classification of drugs of abuse in terms of total harm scores-2.

- Most harmful drugs =100, no harm=0.
- 1. Alcohol,72;heroin,55,crack cocaine,54.
- 2.Methamphetamine,33;cocaine,27;tobacco,26;amphetamine,23.
- 3.Cannabis,20;GHB,19;benzodiazepines,15;ketamine,15;methadone,14; mephedrone,13.
- 4.Anabolic steroids,10;.khat,9,MDMA (ecstasy),9;buprenorphine,7,LSD,7; psilocybin (magic mushrooms),6.
- Note: No relationship ( correlation 0.04) between Misuse of Drugs Act and ISCD classification!

# Magnitude of the problem of drug abuse.

- USA: 29 million adults used illicit drugs at some time; 5.4 million become substance abuse dependent.
- In England and Wales, 11 million (age group 16-59) used illicit drugs; 3.2 million used more than one drug in past year [cannabis < cocaine < ecstasy].
- More men than women used stimulants and class A drugs.
- Deaths related to drug misuse in England and Wales, 2007 Report, 1600. These figures do not include alcohol and nicotine related deaths!

# What do drugs of abuse do?-1.

- Binge/ Intoxication: trigger a large increase in extracellular dopamine in limbic regions of the brain. Imaging studies show that this is associated with reward experiences [pleasure, euphoria]. The subjective experience is due to a rapid, not slow, change in the dopamine concentration.
- This means that the fast delivery of the drug to the brain is important for a rewarding effect.



# Summary of the patho-physiology of addiction.

- 1. The main brain regions and neural circuits are disrupted and contribute to the complex phenotype seen in addicts.
- 2. Some of these changes are specific to certain types of drugs of abuse.
- 3. For example, decrements in dopamine transporter in striatum seen after amphetamine but not after cocaine or alcohol. However, decreases in D2 receptors and activation of CRF pathways seen after all drugs of abuse.
- 4. The final outcome reflects the genetic, developmental and environmental characteristics of the individual.

# Psychopharmacology of drugs of abuse-CANNABINOIDS-1.

- Obtained from Cannabis sativa-main active ingredient is tetrahydrocannabinol (THC).
- Herbal cannabis-8%;resin-20-40%;oil-60%
- THC is a non nitrogen containing molecule;in cannabis smoke, 50% of the THC is bio-available.
- THC activates CB1( in motor,limbic,autonomic and endocrine areas) and CB2 (in GIT and on immune cells).

# Cannabis abuse-1.

- Apart from alcohol and tobacco, cannabis is the most widely abused drug in Europe, America and Australasia.
- Cannabis is used by approximately 181 million adults world-wide. In USA, New Zealand and Australia, used by 42% adults. In Japan and China, cannabis abuse virtually non-existent.
- Nearly equal gender use of the drug.
- Genetic programming of cannabis plant led to marked increase in active ingredient, tetrahydrocannabinol (THC) and a decrease in the endogenous antagonist, cannabidiol.

# Psychopharmacology of drugs of abuse-CANNABINOIDS-2.

- Endogenous ligands for cannabinoid receptors- 2-arachidonylglycerol and anandamide. These transmitters are released from both synaptic and non-synaptic regions.
- Effects- pain modulation (rat model of neuropathic pain) by increasing opioid peptide release and dopamine release in PFC. Also neuroprotective by reducing glutamate release.
- Cause psychological dependence; trigger schizophrenia, depression and anxiety attacks.

## Cannabis abuse-2.

- THC concentration increased from 5% in 1993 to 20-25% in 2008.
- Cannabindiol (CBD) concentration has decreased from 4% to 1-2% over the same period.
- Cannabis use in adolescents associated with poor cognition. The deficits persist into adult life despite abstinence from the drug.

# Pharmacology of THC-1.

- THC is an agonist at CB-1 receptors in the brain and CB-2 receptors in the periphery.
- In the striatum, THC releases dopamine.
- Normally, medium spiny neurons in the striatum are connected by dopaminergic synapses that fire at a regular rate.
- Novel events disrupt this regular firing allowing new synaptic contacts to be formed thereby facilitating learning.
- THC causes chaotic firing of spiny neurons leading to abnormal new synaptic contacts. This is associated with the abnormal thoughts etc and forms the basis of hallucinations and delirium.( Bhattacharyya et al.2009/10

# Pharmacology of CBD-1.

- Acts as a THC antagonist at CB-1 sites.
- In amygdala, THC increases response to fearful faces; this is antagonised by CBD.
- In verbal recall tasks, THC increases striatal activity but CBD decreases it.
- For response inhibition tasks, CBD increases hippocampal function while THC decreases it.
- THC increases both PANSS (+) and (-) scores while CBD has no effect.

# Pharmacology of CBD-2.

- CBD of potential therapeutic value in treatment of schizophrenia. Efficacy demonstrated in a double-blind trial against amisulpride.
- Mode of action NOT due to CB-1 receptor antagonism but in vivo the antagonism correlates with increased anandamide levels.
- Anandamide is an endocannabinoid that enhances neuroplasticity and synaptogenesis.
- CBD also inhibits the  $\alpha$ -7 nicotinic receptor, and activates the TRPV-1 channel to modulate pain. The antipsychotic effect may be linked to a reduction in 5HT<sub>1A</sub> receptor activity.



# Psychopharmacology of drugs of abuse-ALCOHOL-1.

- Pharmacokinetics:-widely distributed in body water.
- 90% oxidised in liver by alcohol dehydrogenase (1) and aldehyde dehydrogenase(2).
- $\text{CH}_3\text{CH}_2\text{OH} > (1) > \text{CH}_3\text{CHO} > (2) > \text{CO}_2 + \text{H}_2\text{O}$ .
- Non tolerant person oxidises 10-15ml absolute alcohol per hour. Alcohol metabolised by zero order kinetics;the more you drink, the slower the metabolism.

# Psychopharmacology of drugs of abuse-ALCOHOL-2.

- Daily intake of 1-2 units of alcohol rapidly leads to tolerance.
- Recommended “safe” intake is 21 units/week for a man and 14 units/week for a woman.
- Psychological tolerance develops more rapidly than metabolic tolerance ; a cause of death through overdose.
- Reverse tolerance- a small dose leads to aggression in the alcoholic.

# Psychopharmacology of drugs of abuse-ALCOHOL-3.

- Mode of action:- Meyer (1901)-alcohol disrupts lipid membranes. This forms the basis of the membrane fluidity hypothesis.
- Alcohol has a selective effect on membrane function (  $\text{Ca}^{++}$  stores, Na/K ATPase, MAO-B activity).
- Alcohol enhances GABAergic function; alcohol sensitive site on GABA-A receptors.
- SSRI's block environmentally linked alcohol tolerance.

# Psychopharmacology of drugs of abuse-ALCOHOL-4.

- Treatment:-
- Acamprosate-reduces craving; reduces NMDA-glutamate function.
- Naltrexone-opiate antagonist that reduces opiate receptor enhancement of cortical dopamine release.
- Disulfiram-aversive conditioning ;toxic effects of acetaldehyde due to inhibition of aldehyde dehydrogenase.

# Novel psychoactive drugs of abuse.

- In order to circumvent the legal restrictions ( as defined by the United Nations 1961 Narcotics Act) on the free availability of drugs of abuse, there has been a dramatic increase in the availability of psychoactive compounds which have similar, and often more potent, properties to the stimulants, opioids, cannabinoids and hallucinogens. These drugs are openly sold in “head shops” in most countries in Europe.
- Because of the serious adverse effects of many of these drugs, laws have been passed to prevent their distribution and sale. However, illegal synthesis of such compounds continues, aimed primarily at adolescents and young adults.

# Types of novel psychoactive drugs.

- 1.Synthetic cannabinoids, known as “spice packages” with higher affinity for CB-1 receptors than THC and often combined with NMDA glutamate antagonists and MAO inhibitors to enhance the effects.
- These drugs cause auditory and visual hallucinations, hypotension, tolerance and dependence. Acute kidney failure and stroke reported!
- 2.Synthetic cathinones (Khat-like) with amphetamine properties. Mephedrone widely available until recently. Causes euphoria, delirium, hallucinations, aggression and seizures.
- 3.Synthetic opioids, such as doxylam and AH-7921, equipotent with morphine. Ketamine-like analgesics with similar side effects to major opioids.

# Novel psychoactive drugs-2.

- 4.Synthetic cocaine-like drugs, such as RTI-111,inhibit monoamine uptake with 5 fold greater potency than cocaine with similar properties and adverse effects.
- 5.Novel tryptamine derivatives, like psilocin and bufotenin .Hallucinogens (5HT2A agonists) with SSRI-like properties. Cause mood lability and anxiety.
- 6.GABA A/B agonists, such as gamma hydroxybuturate and gamma butyrolactone. Phenibut, used as nootropic, anxiolytic and alcohol withdrawal in Russia!
- 7.Ketamine-like analgesic/anaesthetics such as methoxetamine. Addictive and can cause seizures.
- 8.Plant hallucinogens from Salvia species and “Kava Kava” from Piper methysticum (South Sea Islands)

# Conclusion: novel psychoactive drugs.

- Internationally, the “on-line” market for psychoactive compounds is developing more rapidly than research into their properties and adverse effects. This is now a major concern for medical and legal authorities in Europe.
- [Schifano et al. World Psychiatry, 14, 15-26, 2015].



# Is there a role for hallucinogens in psychotherapy?

- Recent clinical studies with psilocybin (from magic mushrooms), negative thoughts reversed and positive thoughts recalled.
- In major depression, negative memories and thoughts dominate over positive or neutral thoughts. Psilocybin corrects this.
- fMRI studies show that a single intravenous dose increases inter-regional neural connections. High doses cause synesthesia (colour linked to sound etc.) and hallucinations.
- Thus psilocybin, by increasing new neuronal pathways, decreases the neuronal contacts associated with negative thoughts-a useful adjunct to psychotherapy.

# Pharmacological treatment for addiction-1.

- Replace harmful drug with less harmful drug [eg. methadone for heroin].
- Use SNUS (moist snuff) for tobacco dependence; dramatic reduction in smoking in Sweden!
- Alcohol and naltrexone (u antagonist)
- Rimonabant (CB1 antagonist) in nicotine and opioid abuse-withdrawn due to side effects!
- Acamprosate (weak NMDA antagonist) in alcohol dependence and varenicline( agonist) in nicotine dependence.

# Treatment of drugs of addiction

- STOP DRUG.
- Introduce antagonist or long half-life agonist of drug of abuse [Methadone, Naltrexone, Diazepam, Nicotine patches etc.]
- Withdraw antagonist or agonist slowly.

**THANK YOU!**

**QUESTIONS AND COMMENTS PLEASE.**

