DRUGS OF ABUSE.

COMPILED BY E. N. KAMADI

BY DR. KUBO

1. DRUG ADDICTION AND ABUSE (PHYSICAL AND PSYCHOLOGICAL DEPENDENCE)

DEFINITIONS

- Substance abuse: chronic or habitual use of any chemical substance to alter states of the body or mind other than for medically warranted purposes
- Dependence: characterized by both tolerance and occurrence of withdrawal syndromes once a drug is stopped. Also known as **physical dependence**
- Addiction: Compulsive, relapsing drug use despite negative consequences. It is at times triggered by cravings that occur in response to contextual cues. Also known as **psychological dependence**

WITHDRAWAL SYNDROME

- Abrupt termination of a drug in a physically dependent person
- Appearance of various signs and symptoms – **characteristic** of the category drug
- Occurs due to:
  - Removal of the drug of dependence
  - CNS hyper-arousal owing to re-adaptation to the absence of the drug of dependence

TOLERANCE

- Reduction in response to the drug after repeated administrations
- **Pharmacokinetic tolerance:** Changes in distribution or metabolism of a drug after repeated administration such that a given drug produces a lower blood concentration than the same dose did on initial exposure.
- **Pharmacodynamic tolerance:** Adaptive changes that have taken place within systems affected by the drug so that response to a given concentration of the drug is reduced.
- **Reverse tolerance = sensitization:** Increase in response with repetition of the same dose of the drug
- **Cross tolerance:** When repeated use of a drug in a given category confers tolerance not only to that drug but also to other drugs in the same structural and mechanistic category e.g. Barbiturates & BDZs; Amphetamine & Cocaine.

SPECTRUM OF PSYCHOACTIVE SUBSTANCE USE

1. • **Beneficial use**
2. • **Casual/Non-problematic:** Recreational, casual or other use that has negligible health or social effects
3. • **Problematic**
4. • **Chronic dependence**

EFFECTS

- Social effects
- Economic effects
- Medical effects
- Addiction

CONSUMPTION OF VARIOUS DRUGS

- Marijuana
- Cocaine
- Sedatives
- Hallucinogens
- Nicotine
- Alcohol

DRUG USE TERMS

- **Illicit drug:** Illegal drugs e.g. cocaine, heroin
- **Recreational drug**: Used for leisure e.g. methamphetamine
- **Adulterant:** Drug added to mimic or enhance the effect f the drug being offered e.g. amphetamines mixed with caffeine
- **Diluent**: Compounds such as sugars or baking soda used to increase the bulk of the drug sample

SYMPTOMS OF SUBSTANCE DEPENDENCE

- Failure to fulfil major role obligations at work, school or at home
- Recurrent drug use in situations where it is physically hazardous
- Recurrent drug-related legal problems
- Recurrent use despite persistent social or interpersonal problems

RISK FACTORS

- Biologic predisposition
  - Patients with genetic polymorphism in the genes that code for aldehyde dehydrogenase are less likely to abuse alcohol due to a resultant disulfiram like reaction
  - Gender; males are more predisposed to abuse alcohol
  - Mental disorders are at high risk of substance abuse
- Environmental factors
  - Chaotic home where drug abuse is prevalent; peer influence
- Drugs
  - Availability, affordability, effect of the drug, available route of administration
- Brain mechanisms
  - Lead to addiction

ADDICTIVE DRUG OF ABUSE

ADDICTIVE DRUGS

- Activate the **mesolimbic dopamine system**
- Divided into 3 classes according to their molecular target:
  - Those targeting GPCRs
    - Opioids, Cannabinoids, Gamma-hydroxybutyric acid (GHB), Mescaline, Psilocybin.
  - Those targeting ionotropic receptors and ion channels
    - Alcohol, Nicotine, BDZs.
  - Those targeting the dopamine transporter systems
    - Cocaine, Amphetamine, Ecstasy

MESOLIMBIC PATHWAY

- It is the **reward pathway**
- Dopaminergic
- Begins in the ventral tegmental area (VTA) of the midbrain and connects to the nucleus acumbens
- Central role in the neurobiology of addiction
- Functions:
  - Reward/motivation
  - Pleasure
  - Euphoria
  - Compulsion

NON-ADDICTIVE DRUGS

INTRODUCTION

- Alter perception and they cause sensation of reward and euphoria without causing addiction
- Primarily target cortical and thalamic circuits
- Include hallucinogens such as LSD (Lysergic acid diethylamide) & phencyclidine and dissociative anesthetics such as ketamine

BY DR. KUBO

2. ADDICTION TO CNS DEPRESSANTS: ETHANOL, BENZODIAZEPINES & NICOTINE.

ADDICTION TO ETHANOL

PHARMACOLOGY

- Complex
- Alters function of several inotropic receptors and ion channels:
  - GABAa receptors
  - Kir3/GIRK channels
  - Adenosine reuptake (through a nucleoside transporter, ENT1)
  - Glycine receptor
  - NMDA receptor
  - 5-HT 3 receptor

HOW ALCOHOL ATTACKS THE BRAIN

1. Alcohol affects the forebrain and assaults motor coordination and decision making
2. Alcohol then knocks out the midbrain and you lose control over emotions and increase chances of a blackout
3. Finally alcohol batters the brainstem as it affects HR, body temperature, appetite and consciousness; a dangerous and potentially fatal condition.

POTENTIAL LONG-TERM EFFECTS OF ETHANOL

- **Small to moderate consumption**
  - Systemic: Increases insulin sensitivity; lower risk of diabetes
  - Brain: Reduce the number of silent infarcts
  - Blood: Increases HDL; Decreases thrombosis; Reduces fibrinogen; Increases fibrinolysis; reduces artery spasm from stress; Increases coronary blood flow
  - Skeletal: Higher bone mineral density
- **Small and large consumption**
  - Joints: Reduced risk of rheumatoid arthritis
  - Gall bladder: Reduced the risk of developing gall stones
  - Kidney: Reduced risk of developing kidney stones

CONT.

- **Large consumption**
  - Brain
    - Impaired development; Wernicke-Korsakoff syndrome; Vision changes; ataxia; Impaired memory; psychological; cravings; irritability; anti-sociality; depression; anxiety; panic; psychosis; hallucinations; delusions; sleep disorders
  - Mouth, trachea and esophagus – cancer
  - Blood – megaloblastic anemia
  - Heart – alcoholic cardiomyopathy
  - Liver – cirrhosis, hepatitis
  - Stomach – chronic gastritis
  - Pancreas – pancreatitis
  - Peripheral tissues – increased risk of diabetes type 2

TOLERANCE, DEPENDENCE, WITHDRAWAL – ALCOHOL ABUSE

- Acute tolerance soon after administration of alcohol
- Chronic tolerance due to altered metabolism
- Cross tolerance with BDZs
- Withdrawal syndrome is common and sometimes severe

FEATURES OF ALCOHOL DEPENDENCE

- 6-12 hours after cessation of heavy drinking – features of withdrawal noted:
  - Tremor (mainly of the hands)
  - Nausea and vomiting
  - Excessive sweating
  - Agitation
  - Anxiety
- 12-24 hours after cessation – visual, tactile and auditory hallucinations
- 24-48 hours after cessation – generalized seizures
- 48-72 hours after cessation – delirium tremens; hallucinations, disorientation & autonomic instability. 5-15% mortality.

MANAGEMENT OF ALCOHOL WITHDRAWAL

MANAGEMENT OF ALCOHOL WITHDRAWAL

- Objectives: Prevention of seizures, delirium and arrhythmias
- Ensure K+, Mg and phosphate balance
- Thiamine to prevent Wernicke-Korsakoff syndrome
- **Detoxification:**
  - Involves substitution of a long acting sedative hypnotic e.g. BDZs for alcohol
  - Long acting agents e.g. Chlordiazepine and diazepam usually used
  - Short-acting drugs e.g. lorazepam and Oxazepam preferred in patients with liver dysfunction
  - Rapidly converted to inactive water-soluble metabolites that will not accumulate
- **Adjuncts to management of alcohol**
  - Psychosocial support/counselling/rehabilitation
  - Medical adjuncts:
    - Naltrexone
    - Acamprosate
    - Disulfiram

NALTREXONE

- Long acting opioid antagonist
- Link shown between alcohol consumption and opioids in experimental studies
- Reduces rate of relapse back to alcohol dependence
- Reduces craving for alcohol

ACAMPROSATE

- Stabilizes the chemical balance in the brain that was disrupted by alcoholism, possibly by blocking NMDA receptors, while GABA type A receptors are activated
- Reduces symptoms of protracted withdrawal e.g. insomnia, anxiety, restlessness & dysphoria
- Helps maintain abstinence for weeks to months, more effective in patients with severe dependence

DISULFIRAM

- Inhibits aldehyde dehydrogenase
- Flushing, throbbing headache, nausea, vomiting, sweating, hypotension & confusion occur within a few minutes after an individual taking disulfiram drinks alcohol
- Poor compliance

ADDICTION TO NICOTINE

INTRODUCTION

- One of the most addictive drug
- Relapse after attempted cessation very common
- Nicotine exposure is via smoking, chewing and snuffing tobacco
- **Tobacco**
  - Mechanism:
    - Enters bloodstream –> stimulates adrenal glands –> adrenaline –>stimulates CNS – increased BP, respiration & HR
    - Leads to release of glucose – suppressed insulin excretion – chronically elevated blood glucose
    - Increases level of dopamine
    - Addiction results from long term brain changes

CIGARETTE SMOKE

- Butane
- Cadmium
- Stearic acid
- Hexamine
- Toluene
- Nicotine - insecticide
- Ammonia – toilet cleaner
- Methanol – rocket fuel
- Carbon monoxide
- Arsenic - poison
- Methane – sewer gas
- Acetic acid - vinegar

PHARMACOLOGY

- Nicotine is a selective agonist of nAChRs
- Rewarding effect of nicotine requires involvement of the VTA in which nAChRs are expressed on dopamine neurons
- When nicotine excites projection neurons, dopamine is released in the nucleus acumbens, thus fulfilling the dopamine requirement of addictive drugs.

- **Nicotine withdrawal:**
  - Irritability
  - Sleep problems
  - Attention difficulties
  - Increased appetite
  - Powerful craving for tobacco

RX OF NICOTINE ADDICTION

- Nicotine substitution
  - Gum
  - Trans-dermal patch
  - Nasal spray
- All these do not achieve peak nicotine level – but suppress the withdrawal symptoms
- Also eliminate exposure to toxic smoke constituents

VARENICLINE

- PA of nicotinic receptors (alpha 4 beta 2 subtype) thought to be involved in the rewarding effects of nicotine
- Blocks the ability of nicotine to activate dopamine
- Interferes with the reinforcing effects of smoking, thereby reducing cravings and supporting abstinence from smoking.

BUPROPION

- Originally marked as an anti-depressant
- Has mild stimulant effects through blockade of the reuptake of catecholamines, especially NE and dopamine
- Suppresses tobacco craving and promotes cessation without concomitant weight gain as is seen with varenicline

ADDICTION TO BENZODIAZEPINES

INTRODUCTION

- BDZ abuse most often occurs concomitantly with other drugs e.g. to attenuate anxiety during withdrawal from opioids
- Mild euphoric effect
- **Withdrawal from BDZs**
  - Occurs within days of stopping the medication symptoms include:
    - Irritability
    - Insomnia
    - Phonophobia and photophobia
    - Depression
    - Muscle cramps
    - Seizures
  - These symptoms taper off within 1-2 weeks.

PHARMACOLOGY

- The rewarding effects of BDZs are mediated by alpha 1 containing GABA a receptors expressed on VTA neurons
- Leads to disinhibition of dopamine neurons
- **Treatment**
  - Gradual dose reduction
  - Long acting BDZ can be used for substitute the short acting ones which are abused more often
  - Withdrawal symptoms Rx by **phenobarbitone**
  - Specific antagonist - **flumazenil**

BY DR. GICHUHI

3. ADDICTION TO OPIODS, COCAINE & AMPHETAMINE

OBJECTIVES

- To describe MoA, clinical effects & management

CONT.

- All addictive drugs increase dopamine concentrations in target structures of the mesolimbic projections

OPIOIDS

- Opioids act at 3 GiPCRs
  - Mu, Kappa & Delta opioid receptors

OPIOIDS

- Actions in the VTA:
  - This is the region where the mesolimbic dopamine system begins
  - Mu opioid receptors inhibit GABA neurons
  - Kappa opioid receptors inhibit dopamine neurons
  - This may explain why Mu agonists cause euphoria while Kappa agonists induce dysphoria

COMMONLY ABUSED MU OPIOIDS

- Morphine
- Heroin
- Codeine
- Oxycodone
- Meperidine

HEROIN

- DiacetylMorphine
- Metabolized to morphine
- IV, smoked or snorted

CONT.

- These drugs induce strong tolerance and dependence
- The withdrawal syndrome
  - May be severe – except codeine
  - Intense dysphoria
  - N, V, D
  - Muscle aches, Muscle spasms (patient appears to be kicking)
  - Lacrimation
  - Rhinorrhea
  - Piloerection
  - Sweating
  - Yawning
  - Fever

HEROIN WITHDRAWAL SYNDROME

- The withdrawal syndrome starts 6-7 hours after the last dose
- The withdrawal syndrome lasts 5-7 days
- When opioids are used as analgesics addiction rarely develops
- When taken for recreational purposes they are highly addictive

RX OF WITHDRAWAL SYNDROME

- Methadone for several days
- Eventually taper the dose by 10-20%
- If opioid not available, relief of symptoms
  - Diarrhea with **loperamide**
  - Sniffles – **decongestants**
  - Pain with **NSAIDs** e.g. Ibuprofen
  - **Clonidine** to decrease SNS over-activity
    - Monitor BP
  - **BZDPs** to decrease agitation and promote sleep

CONT.

- IV overdose features:
  - Shallow and slow respirations
  - Miosis (Mydriasis if brain anoxia develops)
  - Bradycardia
  - Hypothermia
  - Stupor or coma
- If not treated rapidly death can result from:
  - Respiratory depression
  - Cardio-respiratory arrest
  - Death

CONT.

- IV heroin
  - Can produce allergic reaction probably due to adulterants
  - Features are:
    - Reduced alertness
    - Frothy pulmonary edema
    - Increased eosinophils in blood

ACUTE TOXICITY

- Support vital signs
  - ABC
- Intubation:
  - Coma (prevents aspiration)
  - Pulmonary edema (positive pressure breathing through mechanical ventilation)
- Prevent further absorption if oral route
  - Activated charcoal – adsorb the opioid and reduce its absorption
  - Gastric lavage

NALOXONE IV OR IM (OPIOID ANTAGONIST FOR ACUTE TOXICITY)

- Reverses the effects of morphine within 1-2 minutes
- Titrate:
  - To reduce respiratory depression and prevent withdrawal syndrome
- Short acting
  - Monitor for 24 hours if heroin overdose
  - 72 hours if methadone overdose

OPIOID ADDICTION RX

- Use long-acting opioid
  - Methadone
  - Levomethadyl acetate
  - Buprenorphine
- This is referred to as substitution therapy
  - Substitute long acting for a shorter acting agent
  - Reduced euphoria and craving
- Drugs + Education + Counselling

METHADONE

- Oral route
- OD therefore supervised intake is possible
- Abrupt termination invariably precipitates a withdrawal syndrome
- i.e. the patient on substitution therapy remains dependent
- Methadone Rx is for 6-12 months then taper by 5% weekly

NOTE

- Substitution of heroin with heroin is done in some countries
- This is done in controlled settings
- Access to counselling

BUPRENORPHINE

- Oral & Sublingual route
- A PA
- +/- Naltrexone
  - Prevents abuse if dissolved for IV abuse

DRUG FREE PROGRAMS

- No long term methadone
- Support groups
- Counselling:
  - How to cope with stress
  - How to address
    - Craving
    - Easy access to drugs
    - Lack of motivation etc.

USES OF OPIOIDS

- Cancer patients:
  - Can be used for severe pain
  - Fear of addiction is less important
- For chronic opioid medication
  - Use oral route
  - Slow onset of action
  - Long duration of action

OPTIONS FOR THE CANCER PATIENT:

- Methadone – long acting
- Controlled - release oral morphine
- Controlled – release Oxycodone
  - Has been given to patients for controlled of pain and if broken and injected IV it acts quickly hence propensity for abuse
- Long-term Rx with opioids should be used only after other alternatives have been exhausted e.g. NSAIDs
- Suspect abuse in patients on chronic pain treatment in the patient if they:
  - Return for a new prescription earlier than scheduled
  - Visit emergency rooms of different hospitals complaining of acute pain and asking for an opioid injection

COCAINE

- Highly addictive
- Found in the leaves of **Erythroxylon coca**
- Clinical use:
  - Use as a LA (inhibits voltage gated Na+ channels in the PNS)
  - To dilate pupils in ophthalmology
- Early descriptions of cocaine by the South American Indians:
  - It `satisfies the hungry, gives new strength to the weary and exhausted and makes the unhappy forget their sorrows`

ROUTES OF ADMINISTRATION

- IV
- Nasal snorting
  - 3-5 minutes to alter mood
- Inhaled
  - `cracked cocaine` is smoked
  - It is produced by heating cocaine HCl in an alkaline solution to transform it into the free base
  - It is rapidly absorbed in the lungs -> brain
  - Rapid onset of action, 8-10 seconds
- Peal effects in 10-20 minutes
- Duration of action is approximately 1 hour
- Metabolized by esterases
- Excreted in urine
- Tolerance develops
- May need cocaine 2-3 times per hours
- Alcohol: Moderates ‘high’ and dysphoria

MOA

- CNS effects
  - Blocks transporters for the uptake of Dopamine, Noradrenaline and Serotonin
  - Increased dopamine concentrations in the nucleus accumbens
- It activates the SNS:
  - Acute increases in BP, PR
  - Ventricular arrhythmias
  - Loss of appetite (satisfies the hungry)
  - Hyperactivity
  - Insomnia
- Increased risk of:
  - Intracranial haemorrhage, stroke, myocardial infarction & seizures

COCAINE OVERDOSE

- Hyperthermia
- Coma
- Death

- A few exposures to cocaine causes strong cravings for the substance
- Can lead to dependence and addiction
- Causes a withdrawal syndrome
- No specific antagonist is available
- Management of intoxication is supportive

CONT.

- Overdose is a medical emergency
- ICU admission may be needed
- Hyper-adrenergic state
- IV diazepam for seizures
- IV propranolol for ventricular arrhythmias
- Consider intoxication with other drugs e.g. heroin

EFFECTS OF CHRONIC USE

- Paranoid ideation (Paranoia or fear)
- Visual and auditory hallucinations
- Severe depression (‘crashing’) following cocaine intoxication
- Loss of libido
- Impotence and gynecomastia in males:
  - Persist for long periods following cessation of drug use
- Galactorrhea, amenorrhea and infertility in females

CHRONIC COCAINE ABUSE

- Abstinence causes:
  - Depression
  - Guilt feelings
  - Insomnia
  - Anorexia
- Psychotherapy
- Family therapy
- Peer support groups

AMPHETAMINES

- They are ‘club drugs’ as they are used in clubs
- E.g. Amphetamine, methamphetamine
- Are synthetic, indirect-acting sympathomimetic drugs
- They release endogenous biogenic amines such as dopamine and noradrenaline
- They are substrates for monoamine transporters at the synaptic membrane
- They enter cells through these transporters
  - Amphetamine is taken up by DAT where it inhibits the VMAT preventing monoamines from accumulating in the synaptic vesicle
  - The monoamines accumulate in the cytoplasm and are released into the synapse by reverse transportation through the monoamine transporter i.e. the direction of the transporter is reversed.
- There is therefore increased levels of dopamine, NE and serotonin

INCREASED CATECHOLAMINE LEVELS

- Increased catecholamine levels
  - Increased arousal
  - Reduced sleep
- Increased dopamine
  - Euphoria
  - May cause abnormal movements
  - Can precipitate psychotic episodes
- Increased serotonin:
  - Hallucination
  - Anorexia
  - Hyperthermia

CONT.

- Amphetamines are neurotoxic
- Mechanism is not known
- Mediated through the NMDA receptor
- Affects mainly serotonin and dopamine neurons

- **Routes of abuse:**
  - Smoked, oral, IV

EFFECTS

- Increases alertness
- Reduces fatigue
- Agitation
- Confusion
- Bruxism (tooth grinding)
- Skin flushing
- Tachycardia
- Arrhythmias
- Hypertensive crisis – may lead to stroke

CHRONIC USE

- Tolerance may develop
  - Increased dose required
- Withdrawal syndrome
  - Dysphoria
  - Drowsiness
  - Insomnia sometimes
  - Irritability

METHAMPHETAMINE OVERDOSE RX

- Symptomatic
- Ammonium chloride to acidify urine and enhance the clearance of the drug
- Hypertension
  - Sodium nitroprusside
  - Alpha adrenergic antagonists
- Sedatives to reduce agitation
- For chronic methamphetamine dependence:
  - Manage like cocaine

BY DR. M. EZZI

4. ADDICTION TO CANNABINOIDS, PSYCHEDELIC SUBSTANCES & INHALANTS

SCOPE (REFER TO WRITTEN NOTES)

- Cannabinoids
  - Receptors
  - Pharmacological effects
  - Dronabinol
  - Tolerance, dependence, withdrawal & management.
- Psychedelic agents/Hallucinogens
  - Phen-ethyl-amines
    - Mescalin
    - Methylene-dioxy-methamphetamine (MDMA) / Ecstacy
    - Methylene-dioxy-amphetamine (MDA)
    - Dimethoxy-methyl-amphetamine (DOM)
  - Indole-amines
    - LSD
    - N, N – dimethyl-tryptamine (DMT)
    - Psilocybin
- Inhalants
  - Amyl nitrite
  - Anesthetic gases: Nitrous oxide, Halothane
  - Toluene, Gasoline, Kerosene, Carbon tetrachloride.

END