01 - 1. Types of adverse reactions

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Type of reaction Mnemonics Features A: dose-related Augmented e.g., Lithium toxicity – ataxia, coarse tremors, vomiting. B: non-dose related Bizarre Idiosyncratic e.g. malignant hyperthermia, or lamotrigine induced Steven Johnson syndrome C: dose and time related Continuous use Related to cumulative drug use—e.g. long term lithium use and renal damage D: delayed effect Delayed Not due to dose per se but due to the length of use of a medication e.g. tardive dyskinesia in some cases. E: Withdrawal End of use Related to abrupt discontinuation e.g. SSRI discontinuation reaction, opioid withdrawal effects, etc. Tolerance is defined as the need to use increased doses of a drug to maintain a clinical effect. Tolerance is seen for both therapeutic effects and side effect. This may be due to decreased sensitivity of the target receptors due to down-regulation (decrease in numbers in case of agonists), up-regulation (increase in number of receptors in case of antagonists), or reduced responsivity without alterations in receptor numbers. Drugs with similar pharmacological actions can exhibit cross-tolerance e.g. benzodiazepines and barbiturates. Sensitization (aka reverse tolerance) manifests when sensitivity to a drug effect increases over time i.e. the same dose typically produces more pronounced effects as treatment progresses. This is reported with the street use of cocaine. Note that up or down-regulation can be a mechanism of therapeutic effect e.g. in case of SSRIs, the 5HT1A autoreceptors in somatodendritic zones undergo downregulation secondary to increased serotonin availability in the vicinity when reuptake is blocked; this in turn leads to an increase in serotonergic tone of the neurons. Withdrawal: When drugs are administered for a reasonable period of time, a physiological adaptation develops which on withdrawal of the drug can get disturbed and leads to withdrawal symptoms. Abrupt withdrawal of treatment especially for an agent with shorter elimination half-life leads to clinically significant withdrawal symptoms. Hypnotics, opiates, barbiturates, SSRIs, Venlafaxine are some of the drugs associated with discontinuation reaction or withdrawal symptoms. The variables influencing withdrawal symptoms are listed below:

1. Half life Methadone has less withdrawal than heroin as methadone has longer t1/2
2. Range of action Paroxetine has anticholinergic properties; withdrawal causes cholinergic rebound=d symptoms
3. Enzyme interference Paroxetine inhibits its own metabolism via CYP2D6. So withdrawal leads to loss of inhibition Æ excessive paroxetine breakdown Æ sudden steep drop in levels Æ withdrawal symptoms
4. Active metabolites Fluoxetine has active metabolite norfluoxetine with long half-life – hence it produces fewer withdrawal symptoms
5. Rate of withdrawal Slow, gradual tapering is the best. 10% dose reduction every 2 weeks is advocated for benzodiazepines.
6. Co-prescribed drug effects Prescribing an enzyme inducer can reduce the effects of a drug acutely if its metabolism depends on the induced enzyme; Similarly prescribing an antagonist can precipitate withdrawal symptoms. This is the rationale for leaving at least 72 hours before prescribing naltrexone for an opioid detoxified patient.
7. Receptor profile Full agonists on withdrawal produce more discontinuation reactions than partial agonists e.g. clonazepam produces lesser benzodiazepine withdrawal symptoms.

Sustained-release preparations influence the absorption kinetics– not elimination kinetics, hence upon withdrawal, the drop in plasma levels occur at same rate in both XL and plain preparations; e.g. venlafaxine XL has similar discontinuation reaction as venlafaxine normal release. But depot preparations have less withdrawal propensity that corresponding oral drugs.

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