14 - 44_Adverse_Drug_Reactions

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01 - 1. Types of adverse reactions

1. Types of adverse reactions

1. Types of adverse reactions

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.

02 - 2. Mechanism of adverse effects

2. Mechanism of adverse effects

© SPMM Course 2. Mechanism of adverse effects Side effect Receptor Agitation α 2 blockade, 5HT2A/2C stimulation, DRI Akathisia D2 blockade, 5HT2A stimulation (hence some data on mirtazapine, 5HT2A antagonist, reducing akathisia) Delirium Anticholinergic effect (antimuscarinic) EPSE D2 blockade reduces with 5HT2A antagonism Hyperthermia Antimuscarinic action, in serotonin syndrome, may be mediated via 5HT2A/2C Insomnia α 1 stimulation, 5HT2Astimulation (hence SSRIs cause insomnia) Amnesia (memory defects) Anticholinergic effects, GABAA stimulation Hyperprolactinaemia D2 blockade, 5HT1A stimulation Disrupted slow wave sleep SWS is maintained by 5HT2A inhibition; 5HT2A stimulation disrupts sleep architecture Sweating Cholinergic effect and increases with noradrenaline reuptake inhibition Postural hypotension α 1 antagonism Appetite loss 5HT2A stimulation (antihistaminics can increase appetite) GI discomfort, nausea, vomiting 5HT3 stimulation Weight gain 5HT2C antagonism and antihistaminic effects Anticholinergic effects Blurred vision, exacerbation of narrow-angle glaucoma, delirium, and photophobia due to mydriasis, dry secretions, constipation, tachycardia, decreased sweating, urinary retention and hyperthermia. Anorgasmia α 1 antagonism, 5HT2A/2C stimulation (delayed ejaculation in SSRIs). Retrograde ejaculation due to α 1 block, anticholinergic and antihistaminic effects. Tardive dyskinesia Supersensitivity of dopamine receptors, which develops because of prolonged therapy with dopamine-blocking drugs Impotence α 2 blockade, 5HT2A/2C stimulation. 5HT2A/2c stimulation can also reduce libido. Priapism α 1 blockade Obsessions 5HT1D stimulation can induce obsessions. 5HT1A and 2A stimulation reduce OCD. Pathological gambling Habituation of dopamine receptors on repeated use of dopamine agonists (e.g. levodopa) leading to dopamine dysregulation syndrome (DDS)

© SPMM Course Weight gain: No single mechanism can explain the complex metabolic phenomenon of weight gain. Antihistaminic effects, 5HT2A/2C antagonism, insulin resistance (valproate and olanzapine) are noted. Genetic factors seem to involve 5-HT2C receptor. Drugs with a strong 5-HT2C affinity will have a greater impact on body weight of patients with a specific variant of polymorphism of the 5-HT2C receptor promoter regions. Low-potency antipsychotics (chlorpromazine and thioridazine) produce more weight gain and sedation than high-potency agents (haloperidol and fluphenazine).

03 - 3. Antipsychotics adverse effects

3. Antipsychotics - adverse effects

04 - Extrapyramidal effects

Extrapyramidal effects

© SPMM Course 3. Antipsychotics - adverse effects Extrapyramidal effects Acute extrapyramidal syndromes such as acute dystonia, akathisia and parkinsonism are noted with high potency drugs more than low-potency drugs. Tardive dyskinesia and dystonia, perioral tremor (rabbit syndrome) are chronic late side effects. PET studies have indicated that 60%–80% occupation of D2 receptors is associated with antipsychotic efficacy. Higher occupancy levels are associated with an increased risk of acute extrapyramidal symptoms as well as hyperprolactinemia from the blocking of D2 receptors on anterior pituitary mammotrophic cells that normally are tonically inhibited by dopamine produced in the hypothalamic arcuate nucleus. Antipsychotic drugs which have the propensity to induce Parkinsonism (trifluoperazine, chlorpromazine, raclopride, haloperidol, fluphenazine, risperidone) bind more tightly than the endogenous ligand dopamine to D2, while the drugs with low Parkinsonism-inducing propensity (quetiapine, clozapine etc) bind more loosely than dopamine to D2 receptors. Compared to the tightly bound antipsychotic drugs, the loosely bound ones are weaker in potency and thus require higher doses to be clinically effective, but can be titrated faster. These loosely-bound drugs may also dissociate from the D2 receptor more rapidly and could lead to clinical relapse somewhat earlier than the traditional tightly bound antipsychotic drugs (though ths does not seem to be the case for clozapine). Drug-induced parkinsonism is seen in 15-20% of patients treated with antipsychotics, seen within 90 days of treatment (5 to 90) and is characterized by muscle stiffness, cogwheel rigidity, shuffling gait, stooped posture, and drooling. The pill-rolling tremor of idiopathic Parkinsonism is not seen in drug-induced EPSEs - but a regular coarse tremor is seen. Elderly and female are under higher risk. Low potency drugs and those with higher anticholinergic effects cause less EPSEs. It is thought that higher than 80% receptor occupancy of brain D2 by antipsychotics can cause EPSEs. Atypical drugs cause low EPSEs probably due to anticholinergic effects, HT2A antagonism or less avidity of binding i.e. hit and run profile especially for clozapine and quetiapine. Anticholinergics can be used for short period of up to 6 weeks to treat the parkinsonian symptoms. As tolerance can develop for EPSE, the anticholinergics should be withdrawn after 4 to 6 weeks; also, longer chronic anticholinergic prescription increases the risk of TD. The rabbit syndrome is a tremor affecting the lips and perioral muscles and occurs late in the course of treatment.

© SPMM Course Dystonias are brief or prolonged contractions of specific groups of muscles resulting in symptoms such as oculogyric crises, tongue protrusion, trismus, torticollis, blepharospasm. Rarely pharyngeal dystonia can occur resulting in dysarthria, dysphagia, and even respiratory choking. Dystonias occur early in treatment course and can reduce compliance. It is often seen in younger men receiving a high dose of high-potency medications. It is more common with IM administration. Dopaminergic hyperactivity in the basal ganglia occurring when plasma levels fluctuate may be the mechanism behind dystonias. Dystonias show spontaneous

fluctuations, response to reassurance and to anticholinergic drugs. Akathisia includes both subjective and objective - feelings and signs of restlessness. (Possibly due to higher D2 occupancy in striatum). Patients may exhibit inability to relax, jitteriness, pacing, rocking with alternation of sitting and standing. Akathisia can be caused by not only neuroleptics but also antidepressants and sympathomimetics. Dose reduction, changing the drug or adding beta blocker/anticholinergic drugs or benzodiazepines or cyproheptadine are recommended. Akathisia may be associated with an increase in absconsion, suicides and violence if left undiagnosed and untreated in some cases. Tardive dyskinesia is a late side effect occurring in nearly 25% patients usually only after (at least 6 months) 1 – 2 years of treatment. It presents as abnormal, involuntary, irregular choreoathetotic movements of the muscles of the head, limbs, and trunk. Perioral movements are the most common. In some serious cases, patients may have breathing and swallowing muscles involved leading to aerophagia and grunting. TD is exacerbated by stress but is absent during sleep. The absence of insight about the movement disorder is striking in patients. Most cases remit spontaneously. Elderly have a poor spontaneous resolution. Tardive dyskinesia is less likely to remit in elderly patients than in young patients, however. Clozapine can reduce the risk and also treat TD. Dose reduction, withdrawal of the drug, switch to newer atypicals or adding clonazepam can be considered. Neuroleptic Malignant Syndrome Can occur at any time during treatment with neuroleptics RISK FACTORS FOR TARDIVE DYSKINESIA Female gender Elderly Diabetics Previous brain damage Affective illness rather than pure psychotic disorder Children Learning disabled Afro-Caribbean race Long term co-prescription of anticholinergics Frequent drug holidays – will lead to high dose prescription with each relapse

05 - Agranulocytosis

Agranulocytosis

© SPMM Course Consists of the tetrad of extreme hyperthermia, severe muscular rigidity and confusion, and autonomic fluctuations (BP and pulse rate). Patients may be akinetic and mute. Increased WBC count, creatinine phosphokinase, liver enzymes, plasma myoglobin, and myoglobinuria are noted. Subacute onset in 24 to 72 hours, and if untreated lasts 10 to 14 days. More common in young men, after agitation and when using high potency drugs especially in rapid tranquillisation situations. Dopaminergic drugs on withdrawal can produce NMS. The mechanism may be related to dopamine blockade or hypothalamic sympathetic dysregulation. The mortality rate is around 20-30% if untreated and higher if depot is used. Symptomatic management of vital signs instability, fluid replacement and prevention of renal failure secondary to myoglobinuria and prevention of aspiration pneumonia are main treatment methods after immediate stopping of offending psychotropic. Dantrolene, Bromocriptine or amantadine can be used. Low potency or atypical must be used following recovery for an antipsychotic prescription. Agranulocytosis Occurs in around 1 per 100 patients on clozapine. This is 15 to 30 times higher than the risk associated with phenothiazines and olanzapine. The maximum risk is between 4 and 18 weeks, and after a year the risk is same as with phenothiazines. Weekly monitoring of the white cell count is required for 26 weeks in most countries, with the frequency decreasing to biweekly or monthly thereafter. In the UK, yellow, green and red signals are used in WBC monitoring. When a result is red, clozapine must be stopped and never tried again. If yellow, then monitoring frequency must be increased until a green signal is obtained again. Benign neutropenia is common especially in south Asian and Afro-Caribbean race. Lithium can increase WBC count albeit transiently. Some anecdotal evidence supports using lithium in patients with benign ethnic neutropenia in preparation for clozapine use. But lithium and clozapine together can increase the risk of seizures and confusion. Clozapine, when combined with carbamazepine, phenytoin, propylthiouracil, sulfonamides, and captopril, can increase the risk of agranulocytosis further. Paroxetine may precipitate clozapine-associated neutropenia. Many side effects of clozapine such as salivation, sedation, and weight gain, fatigue and lowering of seizure threshold are dose related. But agranulocytosis and myocarditis can occur at any dose.

06 - Sexual dysfunction

Sexual dysfunction:

07 - Other side effects

Other side effects

© SPMM Course Transient leucopenia can occur with typical neuroleptics. But agranulocytosis is the rare effect. Sexual dysfunction: Increased dopaminergic transmission can enhance sexual arousal and penile erection. Hyperprolactinaemia can result in loss of sexual arousal and erectile dysfunction in men; amenorrhoea, reduced sexual desire and hirsutism in women. Antipsychotics reduce sexual performance both directly by reducing dopaminergic transmission and indirectly through inducing hyperprolactinaemia. 43% of those taking antipsychotics report sexual dysfunction at some point, not all of this attributable to the drug. Neuroleptic agents commonly cause ejaculatory problems. Total inhibition of ejaculation (dryejaculation), reduced ejaculatory volume and 'retrograde' ejaculation are the various effects associated with conventional neuroleptics and also clozapine, risperidone and olanzapine. Drug-induced priapism is related to simultaneous α1-adrenergic blockade and anticholinergic activity. The most commonly reported associations are with antipsychotic drugs (20% of all reported priapisms) followed by trazodone. Antipsychotics implicated in this problem include risperidone, chlorpromazine clozapine, olanzapine and thioridazine. The risk is doseindependent and can occur at any time during the course of treatment (duration-independent). Priapism is a urological emergency and can lead to permanent impotence if untreated. Dopaminergic agonist bromocriptine is used to treat sexual dysfunction in men that is associated with hyperprolactinaemia. Other side effects Seizure threshold is lowered especially by low potency antipsychotics. Molindone may be the least epileptogenic. This is a dose-dependent effect. Chlorpromazine is the most sedating typical antipsychotic – mediated by H1 antihistaminic action – tolerance usually develops for this effect. Low potency agents can also cause anticholinergic syndrome (see TCAs). Neuroleptics can decrease cardiac contractility, increase circulating levels of catecholamines, and prolong atrial and ventricular conduction time. Low-potency drugs are more cardiotoxic than high-potency drugs. ECG shows QT and PR prolongation, blunting of the T waves, and ST depression. Thioridazine and droperidol, in particular, can cause torsade de pointes. Antipsychotic related sudden death may be due to cardiac arrhythmias or even seizures asphyxiation or malignant hyperthermia. Drugs causing QT prolongation are associated with more sudden deaths (e.g. thioridazine). Postural hypotension is most common with

© SPMM Course low-potency drugs, and tolerance develops soon. Patients should avoid all caffeine and alcohol, drink plenty of fluid and liberal salt in food. Low-potency drugs can cause weight gain but not as much as is atypical drugs. Nearly 50% of men taking antipsychotics report ejaculatory and erectile disturbances. Thioridazine is particularly associated with decreased libido and retrograde ejaculation in men. Allergic dermatitis and photosensitivity can occur with low-potency agents. Long-term chlorpromazine use can cause blue-gray discoloration of skin areas exposed to sunlight. This is reversible. Irreversible retinal pigmentation is associated with the use of high dose

thioridazine (above 1000 mg a day). An early symptom of the side effect can sometimes be nocturnal confusion associatd to difficulty with night vision. This pigmentation is irreversible and can progress even after stopping thioridazine. Chlorpromazine related pigmentation of the anterior lens and the posterior cornea is seen as whitish brown stellate granular deposits noted in slit lamp – this is benign and not vision impairing. This can resolve gradually unlike thioridazine related retinal damage. Chlorpromazine is associated with cases of obstructive or cholestatic jaundice especially in the first month of treatment associated with rash and eosinophilia. Immediate discontinuation and avoidance of rechallenge are advised. Haloperidol isone of the safest typical antipsychotics in overdose. After an overdose, the electroencephalogram (EEG) shows diffuse slowing and low voltage. QT prolongation: Prolongation of the QT interval is mediated by blockade of the rapid component of the delayed rectifier potassium current (IKr) responsible for repolarisation of cardiac Purkinje cells and myocardial cells. Many drugs, including certain antipsychotics and antidepressants, bind to this potassium channel and thereby decrease the outward movement of potassium. Some antipsychotics – especially droperidol, pimozide, sertindole and thioridazine – have a greater capacity than others to cause IKr blockade. InAdvertent IntraVascular injection event (IAIV) or postinjection delirium sedation syndrome (PDSS) has been described after olanzapine pamoate (long-acting depot) injections. Within 20 min to 3 hours of injection, patients present with sedation, confusion, dizziness, altered speech/dysarthria, and somnolence, symptoms that are consistent with those reported in the case of oral olanzapine overdose. Rarely deep coma may ensue. Medical hospitalization and supportive medical care are usually sufficient to ensure full recovery (usually within 3–72 hours). This effect is linked to accidental punctures of a vessel or injections into a rich capillary bed during administration, leading to quick dissolution and release of free olanzapine. Eli Lilly has recommended a postinjection

08 - Metabolic syndrome

Metabolic syndrome

© SPMM Course observation period of at least 1 - 3 hours in a healthcare facility and to avoid driving or operating heavy machinery in the 24 hours after injection. Metabolic syndrome Metabolic syndrome is a cluster of disorders comprising obesity (central and abdominal), dyslipidaemias, glucose intolerance, insulin resistance (or hyperinsulinaemia) and hypertension. It is highly predictive of type 2 diabetes mellitus and cardiovascular disease. Diabetes Mellitus is twice as prevalent among schizophrenia cohorts than in the general population Unaffected first-degree relatives of patients with schizophrenia share a propensity for type 2 diabetes mellitus (19-30%); this suggests a genetic association between these two disorders Schizophrenia patients have 3 times greater intra-abdominal fat (IAF) than the control group, increasing the risk for metabolic syndrome. In the pre-antipsychotic era over 15% of drug-naïve individuals with first-episode schizophrenia had impaired fasting glucose levels, hyperinsulinaemia and high levels of cortisol. Both typicals and atypicals increase the risk of metabolic syndrome in schizophrenia manifold. But antipsychotics cannot explain all the metabolic dysfunctions noted in schizophrenia. The frequency of metabolic syndrome was 2-4 times higher in a group of people with schizophrenia treated with either typical or atypical antipsychotics. MOST Olanzapine / clozapine quetiapine risperidone ziprasidone aripiprazole/ lurasidone LEAST World Health Organization criteria for metabolic syndrome World Health Organization criteria for metabolic syndrome •Insulin resistance and/or impaired fasting glucose and/or impaired glucose tolerance AND two or more of the following: •Waist - hip ratio >0.90 (men), >0.85 (women) OR body mass index 30 kg/m2; •Triglyceride level 1.7 mmol/l OR high-density lipoprotein <0.9 mml/l (men), <1.0 mmol/l (women); •Blood pressure 140/90 mmHg (or treated hypertension); •Microalbuminuria. (This is not presented in some revised criteria for metabolic syndrome)

© SPMM Course In Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial baseline data (n = 689), the metabolic syndrome was prevalent in 51.6% of female patients and 36.0% of male patients. Females with schizophrenia have a higher risk than males with schizophrenia when compared with a reference population. Mean weight increases during the first year of therapy o 12 to 14lb for clozapine (5 to 6 kg) o 15 to 26lb for olanzapine (7 to 12kg) o 6 to 12lb for quetiapine (2.5 to 5kg) o Up to 5lb for risperidone (2 to 2.5kg) o Less than 2lb for Ziprasidone and aripiprazole For patients with schizophrenia, the best-studied options for weight control include diet and exercise. But controlled behavioral programs for weight reduction in schizophrenia have high dropout rates and are not always accessible. Switch to relatively weight neutral drugs can be considered in resistant cases. CATIE summary CATIE stands for Clinical Antipsychotic Trials of Intervention Effectiveness. The study design was double-blind pragmatic RCT. 1493 patients with chronic schizophrenia (mean duration of illness = 14 years), 57 sites, 2001 to 2004 Olanzapine, quetiapine, Risperidone, ziprasidone (added later in the trial), perphenazine

Primary outcome is a ‘real-world’ measure – discontinuation for any reason, either patient-initiated or physician initiated 76% power to detect 12% difference in primary outcome Irrespective of the prescribed drug – 74% discontinued treatment in 18 months (surprisingly high despite naturalistic design). The median time to stop was 4.6 months. Olanzapine had lowest discontinuation rate (still 64%) – but highest side effect burden. 64% discontinued olanzapine; 75%, perphenazine; 82%, quetiapine; 74%, risperidone; and 79%, ziprasidone. Olanzapine caused most weight gain while quetiapine caused most anticholinergic symptoms; perphenazine had highest EPSE related discontinuation. Those who did not respond after 18 months (those who discontinued for the ineffectiveness of therapy) were re-randomised in phase 2 trial (n=99), and Clozapine was compared to other atypical agents (efficacy pathway). Clozapine had lowest discontinuation rate – median at 10 months. This time-to-discontinuation was nearly 3 times longer than time-to-discontinuation with the other SGAs. Quetiapine had comparatively less EPSEs. As a part of the phase 2 CATIE study (tolerance pathway) those who terminated phase 1 for ‘‘intolerable side effects’’ (444 volunteers) were tested with olanzapine, risperidone, quetiapine, or ziprasidone. Of these treatments, olanzapine and risperidone had equivalent effectiveness, and both were better than quetiapine or ziprasidone by significant but modest margins. CATIE Controversies o Quite complicated study design and many outcomes were analysed from the dataset. o Decisions to add ziprasidone to the protocol was made after recruitment began o Perphenazine was used only in one randomized phase (phase 1) of the study generating controversy.

 o The decision to use double-blinded treatments decreased the resemblance of the study procedures to those of routine clinical care

The mean doses used remain controversial though it is claimed that the study was designed to be pragmatic and not purely experimental. CUtLASS summary: CUtLASS stands for Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study It is an unblinded randomised controlled trial comparing first-generation v. second-generation antipsychotics The primary outcome was the quality of life at 1 year and symptom measures were the main secondary outcome. 1, 227 people with schizophrenia who were being assessed by their clinical team for medication review because of poor response or adverse effects were randomised. The second-generation drugs were amisulpride, olanzapine, quetiapine or risperidone. The rate of follow-up interview was 81% at 1 year. The results showed no advantage of second-generation drugs in terms of quality of life or symptom burden over 1 year with those on first-generation antipsychotic doing relatively better. Participants reported no clear preference for either class of drug. The second phase - CUtLASS 2 trial was of similar design and compared clozapine with other secondgeneration drugs in 136 patients who had not responded well to two or more previous drugs. Results showed that there was a significant advantage for clozapine in symptom improvements over 1 year; moreover, patients significantly preferred it.

09 - 4. Antidepressants adverse effects

4. Antidepressants - adverse effects

10 - Tricyclic agents

Tricyclic agents

© SPMM Course 4. Antidepressants - adverse effects Tricyclic agents Side effects of TCAs are related to anticholinergic, antihistaminic and antiadrenergic properties. Clomipramine is a more selective inhibitor of serotonergic reuptake selective; desipramine is the most noradrenergic selective of TCAs. Amoxapine, nortriptyline, desipramine, and maprotiline have the least anticholinergic activity; doxepin has the most antihistaminic activity. The TCAs are less likely to cause sexual dysfunction and insomnia than the SSRIs. Amitriptyline is associated with weight gain (antihistaminic effect – weight gain can also occur secondary to 5HTc antagonism in other antidepressants). TCAs may cause QT prolongation. Even at therapeutic doses, the TCAs cause tachycardia, flattened T waves, prolonged QT intervals, and depressed ST segment. TCAs are lethal in overdose, causing cardiac arrhythmias and anticholinergic delirium. This may occur 3-4 days after overdose due to the long half-life. No specific antidote available; needs lavage and QRS monitoring. Anticholinergic delirium is characterized by symptoms often described as ‘Mad as a hatter, (confusion, disorientation, visual hallucinations), Hot as a hare (hyperpyrexia), Blind as a bat (loss of visual accommodation), Red as a beet (peripheral vasodilatation) and Dry as a bone (drying of mucous membranes)’. Amoxapine can cause hyperprolactinemia as it has dopamine antagonistic effects. SIADH and hyponatremia can occur with TCAs. Fine rapid tremor and dysarthria are sometimes reported with TCAs. Tricyclic agents such as amitriptyline and imipramine and the nontricyclic agents such as mianserin hydrochloride have been documented to precipitate an attack of angle closure glaucoma. TCA discontinuation: Can cause cholinergic rebound – best to reduce 25 to 50mg per 2-3 days. Discontinuation reaction may occur as early as 48 hours or as late as 2 weeks after discontinuation. Propantheline or reinstitution of withdrawn TCA can reduce cholinergic rebound symptoms.

© SPMM Course NMS vs. serotonin syndrome

NMS Serotonin syndrome Dopamine antagonism and suspected hypothalamic mediated sympathetic overdrive. Excess serotonin availability Onset subacute – days to weeks Sudden minutes to hours onset Resolves in 2 weeks - depending on t1/2 of offending drug Resolves as soon as excess serotonin is reduced – in 24 hours generally No myoclonus Myoclonus prominent Hypomania, not a feature Hypomania may be seen Reflexes normal or absent Hyperreflexia seen Rhabdomyolysis, resultant renal failure and acidosis occur commonly Muscle breakdown not common •Serotonin syndrome is a result of excessive serotonergic transmission in brain. Although no single mechanism appears to be responsible for all of the noted effects, most CNS symptoms are possibly mediated via 5HT 2A receptor stimulation. Mechanism of Serotonin Syndrome Mechanism of Serotonin Syndrome •It is characterized by diarrhea, myoclonus, diaphoresis, hyperactive reflexes, ataxia, hypomanic or labile mood, tremors and disorientation. • It may mimic

NMS or anticholinergic syndrome in those receiving psychotropics. Features of serotonin syndrome Features of serotonin syndrome •Any serotonergic agent on overdose – including SSRI and TCA antidepressants, fenfluramine, LSD, ecstasy, anti-migraine (e.g. sumatriptan) drugs. •High risk with combinations of SSRI and MAOI or RIMA or SSRI themselves, or TCAs especially serotonergic, or SNRI, lithium or l-tryptophan. TCA and MAOI combinations. Tramadol, pethidine, meperidine can also cause serotonin syndrome on combination with the above agents. •Oxazolidinone antibacterial linezolid (which is a reversible non-selective MAOI), tetrabenazine (acts via dopamine and serotonin depletion at nerve endings), entacapone (COMT inhibitor) and selegiline are also implicated. Drugs with high risk of serotonin syndrome: Drugs with high risk of serotonin syndrome: •Withdraw the offending agent •Supportive care: correction of vital signs •Benzodiazepines •5HT2A antagonists: cyproheptadine, atypical antipsychotics, chlorpromazine (? mirtazapine – controversial reports) •In severe cases neuromuscular paralysis and intubation may be required Treatment of Serotonin syndrome: Treatment of Serotonin syndrome:

11 - SSRI antidepressants

SSRI antidepressants

© SPMM Course CPK elevation common; WBC also elevated These laboratory abnormalities are less frequent in serotonin syndrome SSRI antidepressants Nausea, vomiting, anorexia, and diarrhea are common side effects of SSRIs – these are somewhat dose-dependent and can be lessened by dose reduction or a slower titration. SSRIs (similar to TCAs, but less frequently) cause weight gain in up to 30% of patients especially in long-term maintenance phase. During initial treatment insomnia and anorexia are often present. Desensitization and down-regulation of receptors may explain the reversal of the initial SSRI appetitesuppressing effects, which can ultimately lead to weight gain late during therapy. Sexual difficulties such as reduced libido, impotence, ejaculatory dysfunction, and anorgasmia are reported with SSRIs. The incidence of sexual dysfunction is nearly every 1 in 3 patients treated. Akathisia like effects, EPSEs and galactorrhea are rarely reported with SSRIs. Also, fluoxetine is associated with a change in the duration of menstrual period – significance of this is unknown. SSRIs can cause functional impairment of platelet aggregation (thrombasthenia), but not a reduction in platelet number. This can cause easy bruising or prolonged bleeding in those with gastric ulcers or bleeding diathesis. SIADH is also reported; this is often troublesome in alcoholics and the elderly causing hyponatremia, hyperkalemia, hypo-osmolality in serum and increased osmolality of urine. Stopping the offending drug, using demeclocycline and fluid restriction can help. Severe sweating especially nocturnally is seen in some patients; Terazosin is effective in counteracting sweating. Nocturnal myoclonus is reported with SSRIs. The repetitive leg movements occur every 20 to 60 seconds, with extensions of the large toe and flexion of the ankle, the knee, and the hips. Benzodiazepines and levodopa may be tried. In restless leg syndrome, patients complain of creeping deep sensations that cause an irresistible urge to move the legs – disturbing sleep. It is associated with SSRIs and treatment is possible using ropinirole or benzodiazepines and levodopa. Duloxetine, venlafaxine, citalopram, fluoxetine and paroxetine can induce acute angleclosure glaucoma. The pathophysiological mechanism of SSRI –precipitated glaucoma remains unclear; anticholinergic effects or increased level of serotonin, which cause partial pupillary dilation have been implicated. SSRI discontinuation syndrome: The abrupt withdrawal of SSRI especially paroxetine (additional cholinergic rebound) or fluvoxamine (shorter half-life), is associated with a discontinuation syndrome. It usually requires at least 4-6 weeks of treatment before

© SPMM Course discontinuation and resolves spontaneously in 3 weeks. Those who have significant SSRI intolerance during treatment onset will have more discontinuation reactions. Fluoxetine is the SSRI least likely to cause withdrawal syndrome as its metabolite has a long half-life (more than 1 week), producing a slow self-tapering effect in plasma. Fluoxetine in some cases can be used to even treat discontinuation syndrome or to prevent it when stopping another SSRI agent. But a delayed withdrawal syndrome has been reported with fluoxetine in some cases. SSRI

discontinuation syndrome Criterion A Discontinuation or reduction of dose of SSRI after at least 1 month use Criterion B 2 or more of the following seen within 1-7days of criterion A causing significant functional impairment and not due to a general medical condition: x Dizziness, lightheadedness, shock-like sensations (paresthesias), diarrhea, fatigue, gait instability, headache, insomnia, nausea, tremors, visual disturbances Suicide risk and SSRIs: A link between antidepressant use and suicidal ideation among those up to age 24 in short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant drugs has been reported. The average risk of suicidal thinking or behavior during the first few months of treatment in those receiving antidepressants was 4 percent while placebo produces a risk of 2 percent. Ecological studies indicate that since the introduction of large scale SSRI prescription for every 10% rise in prescription 3% decline in suicide rates has happened in certain countries. It is also noted that patients were significantly more likely to attempt/commit suicide in the month before they began drug therapy than in the 6 months after starting it. But the issue still remains controversial, and MHRA has advised against certain SSRI prescriptions in children and adolescents. SSRIs increase the risk of upper GI bleeding especially in the elderly and in those using NSAIDs. SSRIs inhibit the uptake of serotonin into platelets; serotonin is crucial for the haemostatic response of promoting platelet aggregation. Further, SSRIs also increase gastric acid secretion thus elevating the risk of gastric erosion, ulcer and bleeding. Alcohol intake and being positive for H.pylori will also increase the risk of GI bleeding when prescribing SSRIs. Antidepressants with low inhibition of serotonin reuptake (e.g. nortriptyline, doxepin, trazodone) are safer in this regard when compared to those with high inhibition of serotonin reuptake (e.g. clomipramine, paroxetine, sertraline, fluoxetine). Increased serotonergic neurotransmission can adversely affect sexual performance; this explains SSRI-induced sexual dysfunction. Some antidepressants (bupropion, mirtazapine, moclobemide, nefazodone and reboxetine) may be associated with a relatively lower incidence of sexual dysfunction. 5-HT2 antagonists, (e.g. cyproheptadine, mirtazapine), 5-HT1a

12 - Other antidepressants

Other antidepressants

© SPMM Course agonists, (e.g. buspirone) and bupropion (being a dopamine reuptake inhibitor) can reverse sexual dysfunction related to SSRI use. A nitric oxide-dependent second messenger (cGMP) mediates penile vasodilatation. cGMP is eventually broken down by phosphodiesterase type 5 enzyme. Sildenafil is an inhibitor of phosphodiesterase type 5, an action that enhances penile erection in patients with erectile dysfunction. Sildenafil (Viagra) has been tried successfully in the treatment of SSRI-induced erectile dysfunction. The side effects of sildenafil include headaches (most common), dizziness, blurred vision and a blue tinge to vision. Very rarely, persistent painful erection (priapism) can occur. Sildenafil must be avoided by patients with arrhythmias, unstable angina / uncontrolled hypertension.

Other antidepressants Venlafaxine: Sweating is more common than in SSRIs and is treated by terazosin. Significant numbers of patients receiving doses above 300mg/day experience an increase in diastolic blood pressure. This risk is not restricted to those with preexisting hypertension. Mydriasis and exacerbation of angle closure glaucoma are reported with venlafaxine; significant discontinuation reactions are reported due to the shorter half-life of venlafaxine – tapering gradually over 2-4 weeks is recommended. Duloxetine has side effects similar to venlafaxine, but fewer propensities to affect blood pressure. Trazodone is associated with priapism that can be serious if unattended. The first step in the emergency management of priapism is the intracavernosal injection of an alpha1 agonist such as metaraminol or epinephrine. The risk of priapism is greatest during the early phase of treatment. Nefazodone inhibits CYP3A4 and can cause serious hepatic damage and hence not used as often now. Though anticholinergic effects are predominantly absent, alpha1 antiadrenergic effects can produce pseudo-anticholinergic symptoms. Afterimage formation similar to the LSD related tracking phenomenon is reported in up to 12% patients on nefazodone. Both trazodone and nefazodone have a favourable profile for elderly and those with cardiac illness. Bupropion has a very different side-effect profile than the conventional antidepressants. It has no anticholinergic effects, does not cause sedation or weight gain and cause almost negligible sexual side effects compared to other classes of antidepressants. It does not cause orthostatic hypotension or cardiac side effects. It can exacerbate ADHD, eating disorders and tics in those with ADHD. It can enhance sexual activity unlike SSRIs; it increases the risk of seizures in a dose-dependent fashion. Headache, insomnia, dry mouth, tremor, and nausea are the most common side effects of bupropion. Severe anxiety or panic can be exacerbated by bupropion. Due to its effects on dopaminergic neurotransmission bupropion can cause

© SPMM Course psychotic symptoms as well as delirium. Bupropion can cause word-finding difficulties in some patients. Agranulocytosis is reported with mirtazapine use. Hence, signs of infection need to be promptly followed. Buspirone can increase concentrations of haloperidol.

Buspirone + MAOI can cause serotonin syndrome; 2-week washout period is recommended. CYP3A4 inhibitors such as erythromycin, itraconazole, nefazodone and grapefruit juice, increase buspirone plasma concentrations. Buspirone does not cause weight gain, sexual dysfunction, discontinuation symptoms, or significant sleep disturbance. It does not produce sedation. Mianserin and mirtazapine produce drowsiness during the first weeks of treatment but has a low propensity to produce orthostatic hypotension or cardiac effects. Increased weight gain and appetite are also noted while sexual side effects are minimal. 5-HT3 blockade is associated with a reduction in nausea and vomiting; hence to treat depression associated with cancer chemotherapy, mirtazapine is a preferred option. Reboxetine is a noradrenaline reuptake inhibitor (NARI) with negligible serotonergic effects. It has a safe cardiovascular profile and can be used in the elderly. Atomoxetine belongs to the same group but not used as an antidepressant; it is used in ADHD. Reboxetine has a specific side-effect profile linked to the noradrenergic system. Urinary hesitancy has been observed in around 10% of male patients taking part in the clinical trials. Relief from this side effect could be achieved by using tamsulosin, a peripheral alpha1-receptor blocker or doxazosin with a similar mechanism of action as tamsulosin. MAOIs such as phenelzine can induce orthostatic hypotension, pedal edema and insomnia. Apart from cheese reaction, MAOIs can also cause serotonin syndrome in combination with serotonergic agents. Tranylcypromine, and phenelzine to some extent can have stimulating effects leading to insomnia – hence the last dose is best given before 6 PM. Weight gain and sexual dysfunction are also reported. Cheese reaction: o MAOIs and tyramine (and other monoamine) rich foods interact to cause cheese reaction or tyramine reaction. o Tyramine has both direct and indirect (via vesicular release) sympathomimetic actions that develop 20 min to 1 h following ingestion of food. o It is characterized by nausea, apprehension, occasional chills, sweating, restlessness and hypotension with occipital headache, palpitations, and vomiting. o Sympathetic overdrive manifests as piloerection dilated pupils and fever. If severe cerebral hemorrhage and death can occur.

 o In terms of the frequency and severity of the hypertensive crisis, the reversible MAOIs are safer. o Food materials to be avoided include any mature cheese such as Stilton, blue cheese, old cheddar and mozzarella. Fish, cured meats, sausage must be avoided together with mature poultry, wild game etc., liqueurs and concentrated yeast extract. o An MAOI-induced hypertensive crisis can be treated with alpha-adrenergic antagonists such as phentolamine or even chlorpromazine, which is immediately available in most psychiatric wards. This can lower blood pressure in few minutes.

13 - 5. Antimanic agents adverse effects

5. Antimanic agents - adverse effects

14 - Renal effects

Renal effects

15 - Cardiac effects

Cardiac effects

16 - Endocrine effects

Endocrine effects

© SPMM Course 5. Antimanic agents - adverse effects Renal effects Certain side effects including polyuria seems to be associated with peak lithium levels; once daily instead of twice daily dosing can reduce these problems. Nearly 1/3rd of those treated will have this side effect, but tolerance develops in due course; functional antagonism of ADH by lithium ion is considered to be the underlying mechanism. Use of K+ sparing diuretics such as amiloride or spironolactone can control polyuria. Renal damage may occur in severe, prolonged toxicity – but cumulative lithium use rather than toxicity leads more commonly to renal failure in lithium users. Chronic exposure longer than 10 years induces interstitial fibrosis resulting in chronic renal damage. Lithium has a narrow therapeutic index. Lithium toxicity occurs in conditions of overdose or dehydration. Non-specific gastrointestinal symptoms usually precede the more serious neurological symptoms and renal shutdown. Immediate cessation of lithium followed by urgent medical attention is required as some patients may require a hemodialysis if levels exceed 4mEq/L. Topiramate is a weak inhibitor of carbonic anhydrase and can promote the development of renal stones. SIADH may be seen with valproate use though more common with carbamazepine; it is dependent on the dose prescribed. Oxcarbazepine is a 10-keto derivative of CBZ with an identical profile but less enzyme induction and fewer drug–drug interactions. It produces less rash and neurotoxicity but more hyponatremia than CBZ. Cardiac effects ECG effects of therapeutic lithium dose are similar to hypokalemia – with flat T waves, or inverted T. Lithium can depress sinus node activity and so is contraindicated in sick sinus syndrome. Endocrine effects Lithium can cause a variety of thyroid problems – the most common being a benign hypothyroid state. 5% patients may develop goiter, and overt hyperthyroidism is also reported in some cases. Thyroid deficiency is common in those with high risk for preexisting antithyroid antibodies (especially middle-aged women). The risk is 3-4:1 in women and is high in first 2 years of treatment. Rapid cycling patients are at higher risk. High TSH is seen in nearly 1/3rd of chronic lithium-treated patients even in the absence of clinical hypothyroidism. In resistant depression

17 - Haematological effects

Haematological effects

18 - Neurological effects

Neurological effects

© SPMM Course and in non-responsive rapid cyclers with bipolar disorder, using thyroxine to treat subclinical hypothyroidism may be beneficial for the mood disorder. Polycystic ovaries (PCO): 25 - 33% UK population of adult females have PCO morphology notable in ultrasound. 5-26% may have actual PCOD, which is defined as having PCO in ultrasound with hyperandrogenism or LH disturbance. 10% woman on valproate have new onset PCOD. The relative risk is 7.5 for PCOD. On stopping most people remit from PCOD. The exact mechanism by which valproate might causes PCOD remains unknown, although several mechanisms are proposed. For example, valproate increases ovarian androgen production. It also can result in weight gain and insulin resistance, both risk factors for PCOD. In the liver, the drug can increase unbound testosterone. Epilepsy, for which valproate is widely used, is tipped to increase PCOD occurrence. Such association has not been established so far for bipolar disorder. Almost all patients who develop oligomenorrhea develop it in first year of treatment with valproate. Haematological effects Lithium can cause leucocytosis that can be therapeutically utilized in some cases of benign neutropenia related to clozapine use. This is not widely practiced. Around 10% of individuals taking carbamazepine will see gradual onset leucopenia in first 3months of treatment. This is reversible on continued treatment or dose reduction. Thrombocytopenia is a dose-related effect of valproate and carbamazepine – a reduction in dose is required if bruising, or bleeding gums is noted. Neurological effects Fine tremor is a common benign side effect of lithium, and coarse tremor is a sign of toxicity. Propranolol can be used in treating lithium-induced fine tremor at therapeutic levels. Lamotrigine is generally well tolerated but can cause dizziness, ataxia, headache, sedation, tremor, and nausea. Topiramate can produce word finding difficulties (anomia) and poor concentration Vigabatrin, an antiepileptic with no significant antimanic efficiency, has been tried in some openlabel trials. It has a peculiar side effect of causing visual field defects.

19 - Gastrointestinal effects

Gastrointestinal effects

20 - Teratogenic effects

Teratogenic effects

21 - Skin effects

Skin effects

© SPMM Course Gastrointestinal effects Valproate inhibits hepatic enzymes; in some cases the acute liver injury may occur though this is rare in clinical practice. Of persons taking valproate, 5 to 40 percent experience a persistent but clinically insignificant elevation in liver transaminases up to three times the upper limit of normal, which is usually asymptomatic and resolves after discontinuation of the drug (termed ‘transaminitis’). Liver failure is reported with valproate, lamotrigine, topiramate and carbamazepine. Risk factors include young age and combination therapy. This is caused by 2 mechanisms: 1. Metabolic toxicity e.g. due to 4-en valproate, a metabolite of valproate. 2. Hypersensitivity - doseindependent effect is resulting in fulminant failure. Severe hepatic damage associated with valproate is seen especially in those with learning disability when undiagnosed urea cycle disorders are present (less than 2 years often). Another rare side effect of valproate is acute pancreatitis. This is a hypersensitivity reaction; dose reduction will not be helpful. Hyperammonemia can be associated with coarse tremor and carbamazepine co-prescription; it may respond to L-carnitine administration. Valproate competes with carnitine transport and can induce a state of carnitine depletion especially in children and in epileptics. Teratogenic effects The most common teratogenic effect of lithium involves cardiac valves especially Ebstein's anomaly of the tricuspid valves. The risk of Ebstein's malformation in lithium-exposed fetuses is 1 of 1,000 (20 times the risk in the general population). Lithium’s teratogenic effects are somewhat lower than that caused by the use of valproate or carbamazepine. Lithium is excreted into breast milk, and signs of lithium toxicity in infants include lethargy, cyanosis and sluggish neonatal reflexes. Valproate causes neural tube defects as a teratogenic effect in 1% to 4% mothers. Folate-vitamin B complex supplementation for all young women of childbearing potential may reduce risk though it is best to avoid valproate totally. Learning disability and low IQ in children is the most common teratogenic effect of valproate. Skin effects Exacerbation of acne and psoriasis are associated with lithium therapy. Alopecia / hair loss occurs in 5 to 10 percent. It is not clear if zinc and selenium supplementation can reverse or prevent the latter effect.

22 - Weight related effects

Weight related effects

© SPMM Course Valproate can cause obesity, hyperandrogenism and PCOD associated with hirsutism. Anticonvulsant hypersensitivity syndrome is seen in 0.1% of patients taking anticonvulsants. Aromatic compounds (lamotrigine, carbamazepine, phenytoin and phenobarbitone) are especially risky. 5 to 20% of those taking aromatic anticonvulsants will experience a rash. Lamotrigine can cause a rash in 10% of patients. Risk factors for rash include rapid initial dose escalation, concurrent VPA, and age less than 16 years. As benign rashes cannot be distinguished from potentially serious ones, any rash requires discontinuation of the drug. Lamotrigine carries a significant risk of Steven Johnson Syndrome (SJS – risk of 1 in 3000) especially if administered together with Valproate as the enzyme inhibiting effects of Valproate may increase lamotrigine levels. SJS starts with a rash, pharyngitis and fever. Systemic involvement follows quickly if the drug is not stopped.

Drug Dose-related effects Idiosyncratic reactions Carbamazepine Visual disturbances, GI disturbances, cognitive impairment, vertigo and, dizziness. Hematological reactions including agranulocytosis or aplastic anemia, idiosyncratic Stevens-Johnson syndrome, fulminant hepatic damage, and pancreatitis. SIADH is more common in the elderly Valproate Hyperammonemia, Teratogenicity, Sedation, Thrombocytopenia Hepatotoxicity, pancreatitis, rash and rarely acute dermatitis.

Weight related effects Weight gain is common (70% of those taking valproate and 40% of those taking carbamazepine over 12 months will experience weight gain); valproate induced weight gain is considered to be due to impaired beta-oxidation of fatty acids, and thus independent of calorie intake. Lamotrigine is often weight neutral Topiramate is weight neutral and can even cause weight loss. Topiramate can be potentially used to counteract the weight gain caused by many psychotropic drugs.

23 - 6. Other agents adverse effects

6. Other agents - adverse effects

© SPMM Course 6. Other agents - adverse effects Cholinesterase inhibitors: Donepezil causes nausea, diarrhea, insomnia, vomiting, muscle cramps commonly. Rivastigmine causes similar symptoms albeit at a higher frequency of some. Galantamine too has a similar profile. Tacrine is not used anymore in UK due to reports of fatal hepatotoxicity. By increasing central and peripheral cholinergic stimulation cholinesterase inhibitors, can

1. Increase the risk for GI bleeding especially in NSAID users or patients with peptic ulcer.
2. Produce bradycardia, especially in those with supraventricular conduction delay,
3. Exacerbate COPD
4. Cause urinary retention
5. Increase seizure risk
6. Prolong the effects of succinylcholine-type muscle relaxants Rivastigmine's metabolism does not depend on liver P450 enzymes, and, therefore, no drug interactions related to the P450 system have been observed. Memantine does not inhibit or induce hepatic microsomal enzymes; because it is excreted in the urine predominantly as unchanged drug, it is unlikely to be affected by drugs that affect hepatic enzyme function. Stimulants and other drugs used for ADHD: The most common adverse effects are anxiety, irritability, insomnia, tachycardia, cardiac arrhythmias, and dysphoria with decreased appetite. Tolerance usually develops for appetite loss. Less commonly self-limited exacerbation of movement disorders, such as tics and dyskinesias, may occur. Stimulants are linked to growth suppression. Bruxism and restlessness are also reported. Pemoline is associated with fulminant hepatic failure and is no longer used widely. Dependence can occur with methylphenidate though this is rare at doses used for ADHD. Side effects of atomoxetine are appetite loss, sexual dysfunction and dizziness; severe liver injury in has also been reported. Clonidine is not a popular option for treating tics/ADHD due to high rates of hypotension associated with it.

Hypnotics: Overdose of benzodiazepines can produce slurred speech, incoordination, unsteady gait, nystagmus, impairment in attention or memory, stupor or coma and behavioural changes

(inappropriate sexual or aggressive behaviour, mood lability, impaired judgment etc.).

24 - 7. Psychiatric effects of non psychiatric dru

7. Psychiatric effects of non-psychiatric drugs

© SPMM Course High-potency benzodiazepines such as triazolam can cause anterograde amnesia. Paradoxical disinhibition is seen in a few patients especially when preexisting brain damage is present. Triazolam is banned in UK since 1991 following reports of disinhibition and aggression. Benzodiazepines can produce respiratory impairment especially in those with COPD or sleep apnea. Benzodiazepines are better avoided in those with myasthenia gravis, head injury or porphyria due to this risk. Alprazolam can cause weight gain via appetite stimulation. Cleft palate and lips are teratogenic effects associated with benzodiazepines; withdrawal syndrome is seen in a neonate with third trimester use. Z-hypnotics have more potential to cause upset stomach and diarrhea compared with benzodiazepines. Eszopiclone's unique temporary side effect is an unpleasant taste. It can also cause dry mouth especially in the elderly in a dose-dependent fashion. The occurrence of benzodiazepine withdrawal syndrome depends on The duration of treatment, The dosage prescribed, The rate of tapering and The half-life of the compound. Benzodiazepine withdrawal is characterized by anxiety, diaphoresis, kinaesthetic hallucinations, restlessness, irritability, light-headedness, tremor, insomnia, autonomic hyperactivity, and weakness. In severe cases, depression, paranoia, delirium, and grand mal seizures are seen. The syndrome can occur after 1 or 2 weeks in long-acting benzodiazepines. Alprazolam and lorazepam are associated with immediate and severe withdrawal syndrome and should be tapered gradually. Using prescribed benzodiazepines for 4 weeks or less rarely results in significant withdrawal symptoms. But if used for 4 months – 5-10% have withdrawals; in 2 years – 25-45% and in 68years – 75% develop withdrawal syndrome and dependence pattern (Law et al. 2004). Slow taper at a rate of 25% per week, use of longer acting agents when tapering, avoiding longterm use of short-acting benzodiazepines, use of carbamazepine to assist discontinuation are the various strategies employed to manage withdrawal symptoms. 7. Psychiatric effects of non-psychiatric drugs

© SPMM Course Non-psychiatric drugs Psychiatric side effects Beta-blockers Sedation, nightmares, dysphoria (nearly 50% in some samples) and depression. Psychiatric effects are seen only with lipophilic compounds e.g. metoprolol and propranolol. Angiotensinconverting enzyme (ACE) inhibitors Increased arousal, anxiety, fatigue, insomnia and increased psychomotor activity (4-8%) Clonidine Sedation or lethargy (35%); anxiety (3%), agitation (3%), depression (1%), and insomnia

(1%). Nitrates/nitrites Delirium, psychosis (including delusions), anxiety, restlessness, agitation, and hypomania. Digoxin Depression and delirium (even in therapeutic levels) Statins Uncertain association with depression (evidence inconclusive) Corticosteroids Mood changes (mania more than depression), anxiety, agitation, lethargy. Dose-dependent. 1 in 6 patients has psychiatric side effects if prednisolone is prescribed in doses above 80mg/day. Symptoms start within 2 weeks. More common in females and those with past psychiatric history. Anabolic androgenic steroids

Acute paranoia, delirium, mania or hypomania, homicidal rage, aggression, and extreme mood swings, as well as a marked increase in libido, irritability, agitation, and anger. Usually dose-dependent and resolve in 1-4 weeks after stopping the steroids. Gonadotropinreleasing hormone (GnRH) agonists (e.g. leuprolide) Depressive symptoms Interferon-alpha Nearly 40% develop psychiatric side effects; ~20% experience depression. Seen in first 12 weeks of treatment. Penicillin Sedation, anxiety and hallucinations Cephalosporins Delirium Ciprofloxacin and ofloxacin Restlessness, irritability, lethargy, tremors, insomnia, mania, depression, psychosis, delirium, seizures, or catatonia (incidence ≤1%) Isoniazid Delirium, mania, depression, and psychosis. Tetracyclines Depression, insomnia, and irritability at high dosages. Antihistamines and Atropine-like psychosis

 decongestants Proton pump inhibitors & H2antagonists used for peptic ulcer disease Confusion, agitation, depression, and hallucinations— mainly in geriatric patients with impaired hepatic-renal function.

Ondansetron Anxiety Isotretinoin Severe depression and suicidal behavior. Aminophylline and salbutamol Agitation, insomnia, euphoria, and delirium

Depressogenic drugs x Beta blockers x Calcium channel blockers x Interferons (alpha > beta) x Steroids x Cyproterone, progesterone x Varenicline x Isotretinoin x Ezetimibe Rimonabant: Two endocannabinoid receptors CB1 and CB2 are identified; based on the clinical observations of cannabis related increase in appetite (the “munchies”), researchers have studied the involvement of endocannabinoid system in the control of energy balance. Rimonabant, the first of the CB1-receptor antagonists, was developed as an anti-obesity agent on the premise that blocking central cannabinoid activity might reduce food intake. But there is compelling evidence that rimonabant is associated with the development of severe adverse psychiatric events (2.5 times more depression; suicidal ideas and 3 times more anxiety). Animal studies have consistently shown that pharmacological blockade of the CB1 receptor impaired the anti depressant-reducing or anxiety-reducing actions of endocannabinoids. FDA has issued a warning now on the use of this agent.

25 - 8. Prescribing controlled drugs

8. Prescribing controlled drugs

1971 MISUSE OF DRUGS ACT UK Class A drugs: Ecstasy, LSD, heroin, cocaine, crack, magic mushrooms (whether prepared or fresh), methylamphetamine (crystal meth), other amphetamines if prepared for injection o Penalties for possession: Up to seven years in prison or an unlimited fine. Or both o Penalties for dealing: Up to life in prison or an unlimited fine. Or both Class B drugs: Amphetamines, Methylphenidate (Ritalin), Pholcodine o Penalties for possession: Up to five years in prison or an unlimited fine. Or both o Penalties for dealing: Up to 14 years in prison or an unlimited fine. Or both. Class C drugs: Cannabis, tranquilisers, some painkillers, GHB (Gamma-hydroxybutyrate), ketamine o Penalties for possession: Up to two years in prison or an unlimited fine. Or both o Penalties for dealing: Up to 14 years in prison or an unlimited fine. Or both

2001 MISUSE OF DRUGS REGULATIONS Schedule Examples Regulations Coca leaf, cannabis, LSD, mescaline No recognized medicinal use. Supply is limited to research or other special purposes judged to be in the public interest. Requires Home Office licence to possess. Diamorphine, dipipanone, morphine, remifentanil, pethidine, secobarbital, glutethimide, amphetamine and cocaine

Subject to special prescription requirements and safe custody requirements (with the exception of secobarbital). Stock drugs must be recorded in a register that meets the requirements of the 2001 Regulations, and drug stock must only be destroyed in the presence of an appropriately authorized person. The barbiturates (except secobarbital), buprenorphine, diethylpropion, mazindol, meprobamate, pentazocine, phentermine, and temazepam These drugs are subject to the special prescription requirements (except for temazepam) but not to the safe custody requirements (except for buprenorphine, diethylpropion, flunitrazepam and temazepam) or to the need to keep a register, although there are requirements for the retention of invoices for 2 years Part 1 Benzodiazepines (not temazepam) and zolpidem These drugs are not subject to the special prescription requirements or to safe custody requirements. There

© SPMM Course Part 2 Androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin is no need to keep a register, although there are requirements for the retention of invoices for 2 years Weak preparations of drugs usually in other schedules, for example, morphine, codeine Exempt from all controlled drug regulations except the need to keep invoices for at least 2 years All controlled drug prescriptions should have The patient's full name, address and age If a patient is homeless, 'no fixed abode' is an acceptable address The name and form of the drug MUST be written The strength of the preparation, where appropriate The dose to be taken MUST be written The total quantity of the preparation, or the number of dose units, to be supplied in both words and figures A patient identifier number (e.g. NHS number) should be included on prescriptions for controlled drugs Prescriptions must be signed by the prescriber with their usual signature (this must be handwritten) along with GMC number as a good practice The validity period of prescriptions for Schedule 1, 2, 3 and 4 controlled drugs have been restricted to 28 days. Schedule 2 and 3 drugs cannot be prescribed on repeat prescriptions or under repeat dispensing schemes. Patients ideally should collect the controlled drug in person after showing their identification on the first occasion and signing the back of the prescription form. Substitute opioids should be prescribed in daily instalments whenever required. Prescriptions of instalments must specify o The number of instalments o The interval between instalments, o Instructions for supplies at weekends or bank holidays o The total quantity to provide treatment for a period (this must not be exceeding 14 days generally) o The quantity to be supplied in each instalment along with the duration of the instalments to be set out on the prescription, for example 'dispense daily for fourteen days starting on 3rd September 2015'.

26 - 9. ADR Databases

9. ADR Databases

© SPMM Course 9. ADR Databases It is vital that adverse drug reactions (ADRs) that are hitherto unreported are detected rapidly and recorded to reduce the hazards of medical prescribing. Such reports will also trigger regulatory action to ensure further patient safety. MHRA encourages reporting adverse reaction through Yellow Card system even if it is not certain that the drug has caused it, or if the reaction is well recognised, if an overdose has been taken or if other drugs have been given at the same time. Prescribers, patients, carers and pharmacists can all use the yellow card scheme. The black triangle symbol is used to inform that a preparation is newly licensed and requires additional monitoring by the European Medicines Agency. For medicines with the black triangle symbol, the MHRA requires that all suspected reactions (including those that are not serious) be reported. For all other drugs, the yellow cards can be sued to report side effects that are serious, medically significant, or result in harm. Adverse drug reactions that result from a medication error are also reportable using Yellow cards. Term used to describe frequency Rates observed Very common Greater than 1 in 10 Common 1 in 100 to 1 in 10 Uncommon or 'less commonly' in BNF 1 in 1000 to 1 in 100 Rare 1 in 10 000 to 1 in 1000 Very rare Less than 1 in 10 000

WHO established an international system for monitoring adverse reactions to drugs (ADRs) in 1971. This is located at WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, (UMC), in Sweden. The ADRs database held by WHO contains over three million reports of suspected ADRs. Similar reporting systems exist in many other developed nations. The Canada Vigilance Adverse Reaction Online Database and the European Medicines Agency ADR Reporting systems are some examples of other well-developed national/international ADR databases.

Worsening of glaucoma: paroxetine, quetiapine, TCAs Retinal pigmn: Thioridazine Corneal deposits: CPZ Visual field defects: vigabatrin Osteoporosis: hyperprolatinaemic antipsychotics WBC suppression: ^zapines(olanz, mirtaz, cloz, carbama), mianserin Haemolytic anaemia: nomifensine Myocarditis / Pul Embolism: clozapine QT prolong: all antipsychotics esp .Thioridazine, Pimozide, droperidol Arrythmias: high dose TCAs High BP: VFX, TCAs Hypersalivation: clozapine Bruxism: stimulants Hypothyroidism: Li Fine tremors: therapeutic dose of lithium, TCAs Coarse tremors: antipsychotic Parkinsonism, Wt gain: all antipsychotics (less for APZ, ZPD), TCAs, Li, VPA, CBZ Wt loss: Topiramate, Bupropion Guillian Barre: Zimeldine Pedal oedema: MAOIs Cramps: AchEs Orthostatic hypotension: all TCAs, all antipsychotics Priapism: Trazodone, risperidone PCOD: Valproate Erectile dysfunction: all TCAs, antipsychotics Delayed ejacln or anorgasmia: SSRIs Hepatic damage: nefazodone, VPA, tacrine Enz induction: CBZ, phenytoin, barbiturates Ac. Pancreatitis: VPA P.ileus: clozapine GI bleed: SSRIs, AChEs Renal damage: Lithum Nephrolithiasis: topiramate EPSEs: all neuroleptics (less for Anticholinergic neuroleptics e.g. CPZ), higher dose

atypicals Delirium: Anticholinergic TCAs, Anticholinergic antipsychotics Seizures: bupropion, clozapine Tics: stimulants Amnesia: BDZ Rashes, SJS: CBZ, Lamotrigine Thrombocytopenia: Valproate Sweating: all SSRIs, TCAs, esp. VFX Acne, psoriasis: Li Psychotropics Adverse Effects Chart © SPMM Course AchEs: Anticholinesterases, BDZ: Benzodiazepines, CBZ: carbamazepine, CPZ: Chlorpromazine VFX: Venlafaxine VPA: Valproate, SJS: Steven Johnson Syndrome,

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