SIDES EFFECTS OF PSYCHOTROPIC MEDICINES

Introduction

- This section covers the management of some of the side-effects resulting from treatment with psychotropic medication.
- Anaphylaxis, neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are serious side effects of psychotropic medicines. These syndromes constitute a medical emergency and should be dealt with appropriately and/or emergency medical services contacted.
- For full details of the medications included in this chapter including side effects, contraindications, drug interactions and monitoring see the Summary of Product Characteristics available at online at: http://www.medicines.org.uk/emc/ or BNF online at: https://www.medicinescomplete.com/mc/bnf/current/.
- Service users should be encouraged to take part in decisions about their treatment and provided with information about side effects of medicines.

Extrapyramidal Side Effects [EPSE]

- EPSE are usually associated with antipsychotics but can occur with many drugs. They include: acute dystonia, akathisia, drug-induced parkinsonism and tardive dyskinesia

**Acute Dystonia**

- Acute dystonias involve abnormal face and body movements which occur as a result of sustained muscle contractions. They manifest as facial grimacing, tongue dystonia, torticollis (neck), oculogyric crisis (eye), trismus (mouth) or other abnormal posturing.
- Acute dystonias can be frightening for affected service users and can have serious consequences, particularly if pharyngeal, laryngeal and other muscles involved in breathing are affected.
- Risk factors are use of high-potency first-generation antipsychotics, lack of previous exposure to antipsychotic, rapid dose titration and abrupt discontinuation of antipsychotic. Other risk factors include male gender, younger age and substance misuse (e.g. cocaine).
- First line treatment - procyclidine PO or IM for more severe symptoms.
- Second-line treatment - orphenadrine or trihexyphenidyl (benzhexol)
- There are no important differences between the antimuscarinic drugs, but some people may tolerate one better than another.
- Chronic use of antimuscarinic agents is not advised due to side effects and potential misuse.
Akathisia

- Akathisia, a distressing psychomotor restlessness manifested by inability to stay still and feeling agitated, is common with antipsychotics and some antidepressants. It can also manifest during sleep, causing myoclonic jerks.
- Akathisia is dose-related and tends to emerge shortly after starting treatment, especially following high initial dose or rapid dose escalation or parenteral administration or use of high-potency first-generation antipsychotics.
- Other risk factors include males, younger age and substance misuse (e.g. cocaine).
- Use of a second-generation antipsychotic at the lowest effective dose, with gradual dose titration, can reduce the risk of akathisia.
- If symptoms do not improve, switching to an alternative antipsychotic or antidepressant may help.
- Specialists may consider unlicenced use benzodiazepines with long half life (e.g. clonazepam or diazepam) or beta-blockers e.g. propranolol, but contraindications to use of beta blockers must be excluded.

Drug-Induced Parkinsonism

- Parkinsonian symptoms are common and emerge within a few days or weeks of starting an antipsychotic or increasing the dose. Symptoms include difficulty initiating movement (akinesia or bradykinesia), cogwheel rigidity and tremor, most often involving the hands, but also involve the head and other parts of the upper body.
- High doses, old age, female gender and dementia (especially Lewy Body Dementia) are risk factors for drug-induced Parkinsonism.
- Use of second-generation antipsychotics, low dose and switching to an alternative antipsychotic can reduce the risk of Parkinsonism.
- First line treatment - procyclidine PO or IM for more severe symptoms.
- Second-line treatment - orphenadrine or trihexyphenidyl (benzhexol).
- There are no important differences between the antimuscarinic drugs, but some people may tolerate one better than another. Chronic use is not advised due to risk of side effects e.g. dry mouth, constipation, urinary retention and cognitive impairment.

Dyskinesia

- Dyskinesia (acute or tardive) is characterised by diminished voluntary movements and the presence of involuntary movements, similar to tics or choreas, affecting mainly the tongue, face and jaw.
- Tardive dyskinesia (TD) is an uncommon but serious extrapyramidal side effect (EPSE) of antipsychotics. It can occur several months or even years after starting treatment and occasionally, when treatment is stopped. Risk factors for TD include older age, female gender, dementia, previous EPSE, organic brain damage including head injury and use of antimuscarinics.
- Management of TD involves using minimum effective dose of antipsychotic for the shortest possible period, reducing the dose, switching to an alternative antipsychotic, switching from depot to oral medication or discontinuing antipsychotic treatment.
- Tetrabenazine is the only product with a UK licence for the treatment of TD.
Gastrointestinal Adverse Effects

- Gastrointestinal (GI) effects occur commonly with psychotropic medication and can include nausea; vomiting, dyspepsia, constipation and dry mouth.

- Nausea, vomiting and dyspepsia are usually transient and can be minimised by taking medication with or after food or at night. Slow release or enteric formulation may help in some cases. Use of anti-emetics such as metoclopramide and prochlorperazine for nausea and vomiting should be avoided because of the increased risk of extrapyramidal symptoms. Gastroprotection may be necessary e.g. for people taking SSRI antidepressants and NSAIDs who may be at risk of gastrointestinal bleeding.

- Constipation is a common and dose-related side-effect of psychotropic drugs. In rare cases, serious complications such as paralytic ileus and serious intestinal obstruction can occur if constipation is not treated effectively. First line management involves dietary changes (increased daily fibre and fluid intake) and exercise. Use of laxatives may be necessary, particularly during clozapine treatment. The choice of laxative will depend on the nature of the constipation and must take into account service user preferences. Laxatives may be selected from the three main groups, bulk forming, stimulant and osmotic laxatives. See current BNF for details.

- Dry mouth can occur as a side-effect of a variety of psychotropic medications, particularly those with anticholinergic properties. The management of dry mouth involves identification and if possible, correction of the underlying cause. Switching to medication with low or minimal anticholinergic activity or dose reduction, should be considered. Where this is not possible, symptomatic management strategies e.g. healthy diet, strict oral hygiene including regular dentist visits, sucking sugar-free sweets or chewing gum to stimulate saliva flow, adequate hydration, regular sipping of water, and in some cases, use of saliva substitutes may be helpful.

Hypersalivation

- Hypersalivation can occur as a result of treatment with psychotropics, particularly antipsychotics like clozapine.
- When hypersalivation occurs, consideration should be given to reducing the dose of the drug or switching treatments, as appropriate.
- Non-pharmacological methods such as propping up pillows at night, sugar-free chewing gum or sugarless fruit gums may help to increase swallowing of excessive saliva.
- For troublesome hypersalivation, drug treatment may be necessary, but there is little compelling evidence to guide choice of treatment.
- Unlicenced drug treatments most commonly used for drug-induced hypersalivation are hyoscine 150 mcg or 300mg [up to TDS] and pirenzepine 50mg-100mg and atropine eye drops (2 drops on tongue at night) and glycopyrronium 1mg/5ml oral suspension.
Hyperprolactinaemia and Sexual Side-Effects

- Antipsychotics (e.g. first generation antipsychotics, risperidone, paliperidone, amisulpride) and rarely, antidepressants (e.g. paroxetine) can raise prolactin levels.
- Psychotropic-induced hyperprolactinaemia may be asymptomatic but in some cases it can cause menstrual disturbances including amenorrhoea; breast enlargement and galactorrhoea in men and women; reduced fertility and sexual dysfunction.
- Management of hyperprolactinaemia involves monitoring prolactin levels and symptoms, referral for investigations, reducing dose or switching to a drug that is less likely to increase prolactin.
- Specialist referral may also be necessary where treatment of hyperprolactinaemia with dopamine agonists is being considered.
- Sexual dysfunction is an often under-reported side effect of psychotropic medications such as antipsychotics, antidepressants and the mood stabilisers valproate, carbamazepine and lithium. A thorough assessment of underlying causes is essential.
- Spontaneous remission can occur in some cases, but reducing the dose of implicated drugs or discontinuing the causative drug or switching to a different drug may be necessary, where clinically appropriate. The antidepressants mirtazapine, trazodone and moclobemide and the antipsychotics quetiapine and aripiprazole are less likely to cause sexual dysfunction and may be preferred.
- Lifestyle changes such as exercise, weight loss and smoking cessation can also improve sexual function.
- Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil) may be prescribed for erectile dysfunction in specified circumstances but via specialist services only. These medications are not prescribable within Mersey Care NHS Foundation Trust.

Hyponatraemia

- Hyponatraemia has been associated with the use of antidepressants, carbamazepine, and rarely, antipsychotics, particularly in older adults.
- Management of hyponatraemia is guided by the serum sodium level, degree of severity of accompanying symptoms and the state of fluid balance.
- In all cases of low serum sodium, alternative explanations for hyponatraemia should be investigated.
- In mild-moderate hyponatraemia, correction of sodium depletion and any fluid imbalance may be helpful.
- Dose reduction and switching treatments may be tried, wherever possible.
- Plasma sodium levels below 120 mmol/l and symptomatic drug-induced hyponatraemia may require withdrawal of the causative drug and more aggressive therapy with intravenous sodium chloride 0.9%.
- Referral may be required for acute illness or severe and/or refractory hyponatraemia.
- Baseline measurements of electrolyte levels before starting therapy and periodic monitoring of fluid and electrolyte status is advised when psychotropic known to cause hyponatraemia are prescribed.
- Some cases of hyponatraemia can be counteracted by demeclocycline or lithium, but specialist advice is required.
**Weight Gain**

- Weight gain has been associated with the use of many psychotropic medications, including antidepressants (e.g. tricyclics, paroxetine, mirtazapine), antipsychotics (e.g. clozapine, olanzapine, quetiapine) and mood stabilisers (e.g. valproate, lithium and carbamazepine).
- Psychotropic-induced weight gain can affect the physical, social and emotional well being of service users.
- Clinicians need to be vigilant and persistent in monitoring and intervening if weight gain occurs.
- Of the antidepressants, tricyclics, paroxetine and mirtazapine can cause significant weight gain, the extent of which is thought to correlate positively with dosage and duration of treatment.
- Healthy lifestyle, diet and regular exercise may be beneficial.
- Routine clinical use of pharmacological interventions for weight loss is not recommended.
- Dose reduction/switching/stoppage of causative drug should be considered before pharmacological interventions for weight loss.
- Pharmacological treatments may be tried after lifestyle interventions have been fully explored and the other interventions, above, considered:
  - In people at high risk of diabetes, metformin should be considered as an adjunct to attenuate or reduce weight gain following antipsychotic medication (in line with NICE PH38).
  - Orlistat in conjunction with a mildly hypocaloric diet is indicated for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m², or overweight patients (BMI > 28 kg/m²) with associated risk factors. See BNF for further details.
  - Adjunctive aripiprazole has been used for weight gain associated with clozapine and olanzapine.
- Follow NICE guidelines for obesity at [https://www.nice.org.uk/guidance/CG189](https://www.nice.org.uk/guidance/CG189)

**Hyperglycaemia and Diabetes Mellitus**

- Psychotropic medications such as antipsychotics (e.g. olanzapine and clozapine) and antidepressants (e.g. tricyclics and some SSRIs) may be associated with impaired glucose tolerance and diabetes.
- Some psychotropic medicines have also been reported to cause loss of hypoglycaemic awareness.
- All service users with diabetes mellitus or risk factors for diabetes mellitus treated with psychotropic medication should be monitored regularly for signs and symptoms of hyperglycaemia and glycaemic control.
- Frequency of monitoring should be individually determined based on known risk factors. Baseline and annual monitoring of glucose and weight/BMI is recommended.
- Follow NICE guidelines on the prevention of Type 2 diabetes in people at high risk [https://www.nice.org.uk/guidance/ph38](https://www.nice.org.uk/guidance/ph38) and on the management of type 2 diabetes at: [https://www.nice.org.uk/guidance/CG87](https://www.nice.org.uk/guidance/CG87)
Hyperlipidaemia

- Antipsychotics have been associated with hyperlipidaemia. Low-potency typical antipsychotics, clozapine, olanzapine and quetiapine may have a higher risk than high-potency typical antipsychotics (e.g. haloperidol and risperidone or aripiprazole).
- Managing risk factors such as diet and weight, switching treatments and treatment with statins may be necessary.
- Follow NICE guidelines for Lipid modification at https://www.nice.org.uk/guidance/CG181

Cardiovascular Side-Effects

- Use of psychotropic medication may be associated with cardiovascular side effects such as postural hypotension, hypertension, tachycardia, cardiac arrhythmias or ECG changes, stroke/TIs, venous thromboembolism (DVT/PE) and sudden death.

Blood pressure Changes

- Blood pressure should be measured regularly, particularly in older adults and people with cardiovascular disease, when initiating treatment or changing dose. Cautious dose increases and use of lower doses can reduce risk of hypotension and falls/fractures.
- Practitioners should be aware of possible increased hypotensive effects when some antihypertensive medications are combined with antipsychotics.
- Follow NICE recommendations on hypertension at https://www.nice.org.uk/guidance/cg127

Tachycardia

- Tachycardia is usually dose-related and often occurs following rapid dose escalation. Gradual dose titration is advised.
- When tachycardia occurs, reducing the dose or switching treatments may be effective.

Stroke and Venous foembolism (VTE)

- Antipsychotic use may be associated with an increased risk of VTE. The risk of cerebrovascular adverse events, such as stroke or transient ischaemic attacks, may be increased in older people with dementia prescribed an antipsychotic; mortality rate is also raised.
- Risk factors for stroke and VTE should be identified and addressed before and during treatment with antipsychotics.
**QT Interval Prolongation**

- Antipsychotics, some antidepressants (citalopram/escitalopram) and lithium can cause a dose dependent QT interval prolongation, which can lead to ventricular arrhythmias and in some cases life-threatening torsades de pointes and sudden death. Risk factors for ventricular arrhythmias include: congenital long QT syndrome or history of arrhythmias, family history of QT interval prolongation or sudden unexplained cardiac death, bradycardia (heart rate less than 55 bpm), electrolyte imbalance (particularly hypokalaemia or severe hypomagnesaemia), or use of other medicines that affect electrolytes (especially diuretics, but also others), old age, female gender, concurrent use of medicines that prolong QT interval or produce pronounced bradycardia, and cardiac disorders (e.g. recent myocardial infarction and congestive heart failure)
- The probability of QT-interval prolongation is increased if a psychotropic drug is given intravenously or at an excessive dose or if high doses of two or more antipsychotic drugs are used concurrently.
- In people at particular risk of QT-interval prolongation, psychotropic medicines that prolong the QT interval should be either avoided or used with caution and after assessing the ECG and plasma electrolytes. Service users should continue to be monitored for ECG changes and for signs and symptoms of arrhythmias during treatment, particularly when increasing dose or using parenteral therapy.
- Significant QT interval prolongation requires discontinuation of treatment and specialist cardiology advice; any electrolyte imbalance should be corrected. If torsades de pointes or other arrhythmias are identified, emergency treatment must be instituted.
- Service users be advised to report promptly symptoms such as palpitations, dizziness or fainting; ECG should be obtained for these patients and they should be assessed for any signs and symptoms of arrhythmias.

**Suicidal Ideation and Behaviour**

- Emergence of suicidal ideation and behaviour, self harm or unusual changes in behaviour can occur with psychotropic drugs.
- Antidepressants are associated with an initial worsening of anxiety/agitation and an increased risk of suicidal thinking and behaviour. Monitor closely, at 2 weekly intervals, particularly at the start of treatment and when the dose is changed.
- A small increase in suicidal ideation and behaviour has been reported during treatment with antiepileptic drugs for various indications.
- Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal. In some smoking cessation clinical trials, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment. Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.
- Suicide attempts and suicidal ideation have been reported in patients treated with atomoxetine. Stimulants such as methylphenidate carry a caution for risk of suicide. Monitoring for the appearance or worsening of suicide-related behaviour is recommended.
- Suicidality is also associated with psychiatric conditions and may be a side effect of treatment with many other drugs.
- Healthcare professionals, service users and their families/careers are advised to be aware of the risk, and to be alert for mood changes, distressing thoughts behavioural changes and other warning signs that might signal suicidal ideation.
Psychotropic Discontinuation Reactions

**Antipsychotics**
- Suddenly stopping antipsychotic therapy can precipitate a range of symptoms, such as nausea, vomiting, diarrhoea, sweating and headache. Most discontinuation symptoms are mild and self-limiting but persistent reactions may require symptomatic treatment.
- Relatively severe dystonias and dyskinesias may also occur following rapid withdrawal of antipsychotics. A minority of service users may show signs of relapse or a withdrawal psychosis, characterized by delusions, hallucinations, hostility and paranoid reactions, which may be more severe than observed previously. These symptoms are part of a cholinergic rebound, and anticholinergic drugs may help to alleviate such symptoms.

**Antidepressants**
- Withdrawal symptoms may occur on discontinuing antidepressants, particularly after abrupt discontinuation following long-term treatment. Gradual discontinuation by slow dose taper is recommended.
- Commonly reported symptoms include headaches, nausea, dizziness, anxiety, paraesthesias, insomnia and vivid dreams, tremor. Other symptoms may also occur including, vomiting, ‘electric shock’ sensations, ‘flu-like symptoms, agitation, emotional lability, and confusion.
- Most discontinuation symptoms are mild and self-limiting but persistent reactions may require symptomatic treatment.

**Other Side Effects**

**Impaired Vision**
- In susceptible individuals, drugs with antimuscarinic effects such as antipsychotics, antidepressants and antimuscarinic agents may potentially precipitate or worsen glaucoma, blurred vision and mydriasis. Use of the lowest effective dose of medication or switching to alternative psychotropic drugs with little or no anticholinergic effects may help. Discontinuation of treatment usually resolves symptoms.
- Phenothiazines carry a risk of pigmentation of the eye and lens opacities and this is increased with higher doses of phenothiazines and longer duration of use.
- Service users should be advised to seek urgent medical attention should visual impairment occur, particularly symptoms of acute angle closure glaucoma occur.

**Hepatic Impairment**
- Almost all psychotropic drugs including antipsychotics, antidepressants, hypnotics, anxiolytics and anticonvulsants are metabolised by the liver. Psychotropics can cause liver disorders or more commonly, asymptomatic elevations in liver function tests and serum bilirubin.
- Deranged liver function tests could be a sign of hepatic problems, so investigations are necessary to rule out any serious problems.
- A lower starting dose and cautious dose increase is recommended to reduce risk of psychotropic-induced liver disorders.
- Use of depots and psychotropic medication with a long half life should be avoided due to delayed clearance.
- Service users should be informed of the symptoms of liver injury and advised to seek urgent medical advice if symptoms occur.
**Sleep disturbances**
- Insomnia and sedation are common side effects of many psychotropic drugs, particularly at the start of treatment. Some tolerance develops in most cases, but persistent sleep problems can interfere significantly with social functioning and performance of skilled tasks.
- Sedation can be reduced by decreasing the total daily dose, changing the dosing schedule to a single bedtime dose, or changing to a less sedating treatment option may help alleviate this side effect. Medicines which cause insomnia should be given in the morning.

**Seizures**
- Most antipsychotic and antidepressant drugs lower the seizure threshold and should therefore be used with caution in service users with a history of epilepsy or risk factors for seizures.
- Antipsychotic-induced seizures may be managed by dose reduction, switching or exceptionally, use antiepileptic drugs.

**Blood dyscrasias**
- Haematological disorders have been occasionally reported with psychotropics. Agranulocytosis is probably the most important drug-related blood dyscrasia.
- Drugs known to cause neutropenia/agranulocytosis include clozapine, phenotiazines, quetiapine, olanzapine, mirtazapine, valproate and carbamazepine. Drugs known to cause neutropenia should not be used concomitantly with other drugs known to cause this problem. High temperature and other indicators of possible infection should be looked for routinely during treatment.
**Skin Disorders**

- Phenothiazine antipsychotics are often associated with skin reactions (urticaria, pruritis, dermatitis, skin discoloration and photosensitivity) but dermatological side effects can also occur with other antipsychotics. Risk-reduction measures include use of effective sunscreens and emollients. Treatment discontinuation can resolve the problem.

- Certain skin conditions such as psoriasis and acne can be aggravated by lithium therapy.

- Allergic dermatitis and urticaria are very common with carbamazepine. Severe, potentially life-threatening, skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis can occur rarely in association with carbamazepine. The risk of severe skin reactions is increased in people of Han Chinese, Hong Kong Chinese, or Thai origin. Before deciding to initiate treatment, these population groups should whenever possible, be screened for HLA-B*1502 as the risk of carbamazepine-induced Stevens-Johnson syndrome is strongly associated with presence of this allele.

- The presence of the *HLA-A*3101 allele may increase the risk for carbamazepine-induced skin reactions in patients of European descent or Japanese origin.

- The presence of the HLA-B*1502 allele may be associated with an increased risk of developing SJS in individuals of Thai and Han Chinese ethnic origin when treated with phenytoin.

- Skin rashes and serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can occur during treatment with lamotrigine, usually within 8 weeks of starting treatment. The main risk factors for rash include concurrent use with valproate, high initial dose of lamotrigine or exceeding the recommended rate of dose escalation and a history of antiepileptic-induced rash. The majority of rashes are mild and self-limiting and resolve once lamotrigine has been stopped; however, some people have developed permanent scarring and there have been rare reports of fatalities. All service users who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that lamotrigine is not restarted in those who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk. Lamotrigine must not be restarted in any service users who has developed SJS or TEN with previous use of lamotrigine. Rash has also been reported with lamotrigine as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver and aseptic meningitis. This requires immediate treatment discontinuation.
References

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