

Antipsychotics

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(updated by Glenice Bateman, Pharmacist, 2011)

Introduction

Antipsychotics are the foundation of pharmacological treatment of schizophrenia and other psychotic illnesses. Antipsychotic medications reduce positive symptoms such as hallucinations, delusions and thought disorder. They can also have some impact on negative symptoms such as poor motivation, blunted affect and cognitive impairment. Antipsychotics are very important in preventing relapses.

Antipsychotic actions are thought to be mediated by the blockade of dopamine transmission in various parts of the brain. Antagonism of other receptors, such as serotonin and histamine, also influence the activity of antipsychotic drugs.

Clinical Indications

Antipsychotics are prescribed for:

- Schizophrenia
- Delusional Disorders
- Schizoaffective Disorders
- Schizophreniform disorder, brief reactive psychosis or disorder not otherwise specified
- Bipolar Disorder manic or mixed
- Major Depressive Episode with psychotic features
- Organic mental syndrome with psychotic features
- Aggressive/disruptive behaviour in delirium, dementia or mental retardation (low doses)

Major and sub classes

There are two major types of antipsychotics:

1. Conventional or typical antipsychotics
2. Atypical antipsychotics

Conventional or Typical Antipsychotics:

The conventional antipsychotics are divided into several different classes according to their chemical structure:

- Phenothiazines (chlorpromazine, fluphenazine, pericyazine, thioridazine, trifluoperazine)
- Butyrophenones (droperidol, haloperidol)
- Thioxanthines (flupenthixol, thiothixene, zuclopenthixol)
- Diphenylbutylpiperidines (pimozide)

Zuclopenthixol, Haloperidol, Fluphenazine and Flupenthixol are all available in depot preparations. All antipsychotics competitively block dopamine D2 receptors. All conventional antipsychotic drugs are thought to be of equal efficacy when taken at the appropriate dose.

Atypical Antipsychotics

Atypical antipsychotics, or the “newer” antipsychotics, effectively treat psychotic symptoms, but have a lower incidence of extra pyramidal side effects than conventional agents. The atypical antipsychotics have effects on dopamine, serotonin, histamine and muscarinic receptors. Current atypicals in use in Australia are:

- Amisulpride
- Aripiprazole
- Quetiapine
- Olanzapine
- Risperidone
- Clozapine
- Ziprasidone
- Paliperidone Oral

Depot Formulations

Some antipsychotics are also available in long acting or 'depot' formulations. These can be used when there are issues with medication adherence. The use of a small initial test dose is recommended for conventional antipsychotics. After the test dose is administered the patient should be closely monitored for adverse and/or allergic reactions and clinical response to the medication. Extrapyramidal side effects are common and the incidence is the same for all depot formulations. The pharmacokinetics of depot formulations are quite complex and it may take several months for the medication to reach steady state. Oral supplementation of antipsychotics may be required. Depot formulations are usually given at intervals of 2-4 weeks by deep intramuscular injection and deltoid muscle injection is an option with some specific products eg. Risperidone. Doses of depot medications should not be altered for minor reasons over short periods of time, as this can lead to adverse effects or compromise the control of symptoms.

New atypical long acting antipsychotics have become available recently eg. Risperidone, Olanzapine do not require a test dose if oral form of the drug has already been prescribed and administered. A long acting injection form of Paliperidone and Aripiprazole are expected to be available in the near future.

Comparative Information for Anti-psychotics

Antipsychotic	Characteristic
All antipsychotics can cause hyperlactinaemia and EPSE	
Conventional antipsychotics	
Chlorpromazine, pericyazine	Most sedating, most potent anticholinergic effects, least likely to cause EPSE, most likely to cause orthostatic hypotension; sometimes referred to as 'low potency' antipsychotics.
Trifluoperazine, fluphenazine	Moderately sedating; intermediate propensity to cause EPSE, some potential to cause orthostatic hypotension
Haloperidol, droperidol, thiothixene, pimozide	Least sedating, almost no anticholinergic effects, most likely to cause EPSE, least likely to cause orthostatic hypotension; sometimes referred to as 'high potency' antipsychotics.
Atypical antipsychotics	
Atypical agents have less potential for EPSE than conventional agents, but depends on dose	
Amisulpride	Less potential for weight gain and sedation
Aripiprazole	May cause insomnia, less potential for hyperprolactinaemia
Clozapine	Effective in treatment-resistant patients but has serious adverse effects (blood dyscrasias, seizures, cardiomyopathy, myocarditis, orthostatic hypotension, sedation, weight gain)
Olanzapine	Related to clozapine may cause sedation, weight gain, peripheral oedema; increased risk of stroke and related mortality in elderly dementia patients.
Quetiapine	Sedating and vasoactive less potential for hyperprolactinemia
Risperidone, Paliperidone	orthostatic hypotension and hyperprolactinemia, may be a problem; increased risk of stroke and related mortality in elderly dementia patients
Ziprasidone	Less potential for weight gain,

(Reference: Australian Medicines Handbook (2010) Australian Medicines Handbook Pty Ltd)

Administration Considerations

Therapeutic effect

Most antipsychotics are absorbed rapidly and are highly lipid soluble. There is widespread variability amongst patients in the pharmacokinetics of and responses to these drugs. The onset of the sedative properties of antipsychotic medications can be relatively fast, however, the impact on the target positive and negative symptoms may take several weeks. Symptoms often respond to antipsychotics in somewhat different time frames. Agitation, sleep and appetite often respond in the first 1-2 weeks whereas personal hygiene and basic interpersonal socialisation may be slower to respond (2-3 weeks), and psychotic symptoms can gradually decrease over 2-6 weeks. Residual symptoms may continue to improve at 6-12 weeks. An effective trial should be at least 6-8 weeks at doses that are within the prescribed range. Positive symptoms may respond to medication in 1-2 weeks. The lowest dose possible should be prescribed, followed by appropriate dose titration. Atypical and typical antipsychotics are of comparable efficacy, with the exception of Clozapine, which is thought to have superior efficacy. Atypical medications are thought to be better in treating the negative symptoms of schizophrenia and may also have a positive effect on cognitive dysfunction. Because their efficacy is at least equal to the conventional medications and they are relatively well tolerated, the atypical agents are widely advocated as first line treatment.

Interactions

Antipsychotics are involved in various drug interactions via the hepatic cytochrome P450 enzymes. Drugs that induce or inhibit these enzyme pathways can produce clinically significant drug interactions. There are clinically significant drug interactions with many drugs, including alcohol, benzodiazepines, SSRIs, nicotine (smoking) and carbamazepine.

Reading

Therapeutic Guidelines Limited. (2003) Therapeutic Guidelines Psychotropic, Version 5. pp 45-48.

How long antipsychotics should be taken for?

Continuing antipsychotic drugs for at least 6 months after an acute episode reduces relapse rates. Some people will require anti-psychotic medication for long periods. Usually the medication is continued for 1-2 years after the person has achieved excellent recovery from their first episode, and is stable in life with regards to work or accommodation. If the person experiences another episode they may need anti-psychotic medication for 2-5 years before ceasing use. For those who have multiple episodes, they may need to use medication for much of their life. Indefinite continuation of maintenance therapy is required for the majority of people with schizophrenia.

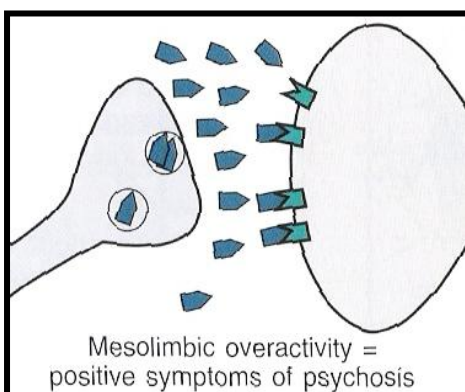


Figure 1: The Dopamine Hypothesis of Psychosis

Overactivity of the dopamine neurons in the mesolimbic pathway may mediate the positive symptoms of psychosis (Stahl, S, (1999) Psychopharmacology of Antipsychotics, Martin Dunitz, London)

Conventional or Typical Antipsychotics

All conventional antipsychotic drugs block dopamine D2 receptors. Antagonism of the dopamine D2 receptor results in the antipsychotic effects. Conventional antipsychotics block dopamine, muscarinic, histamine and alpha-adrenergic receptors.

Typical/Conventional Antipsychotics available for use in Australia

- Chlorpromazine
- Droperidol (use limited due to serious cardiac adverse events and sudden death)
- Flupenthixol Decanoate
- Fluphenazine Decanoate
- Haloperidol
- Haloperidol Decanoate
- Pericyazine
- Pimozide (Available only through Special Access Scheme (SAS) due to serious cardiac adverse effects and sudden death)
- Thioridazine (use restricted due to serious cardiac adverse events and sudden death)
- Thiothixene (Not marketed in Australia but may be available through Special Access Scheme (SAS))
- Trifluoperazine
- Zuclopenthixol Acetate
- Zuclopenthixol Decanoate
- Zuclopenthixol Dihydrochloride

Indications

- Acute Psychosis
- Schizophrenia
- Acute Mania
- Organic Psychosis
- Adjunct in psychotic depression
- Severe behavioural disorders in children
- Adjunct in anaesthesia
- Adjunct in treatment of alcoholic hallucinosis
- Tourette's syndrome
- Intractable nausea and vomiting (haloperidol, droperidol)
- Intractable hiccup (chlorpromazine)

Physiological Action: Conventional or typical Antipsychotics

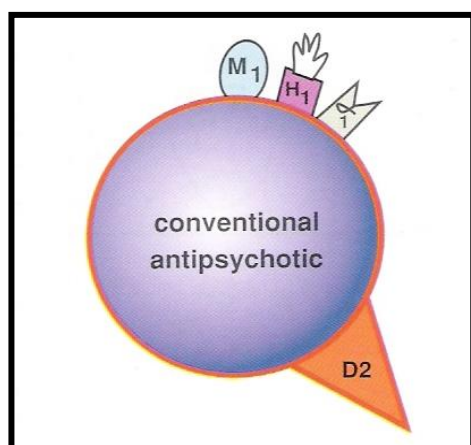


Figure 2: Conventional Antipsychotic

The figure represents a conventional or typical antipsychotic drug. Such drugs have at least four actions: blockade of dopamine, histamine, muscarinic and alpha-adrenergic receptors. (Stahl, S, (1999) Psychopharmacology of antipsychotics, Martin Dunitz, London).

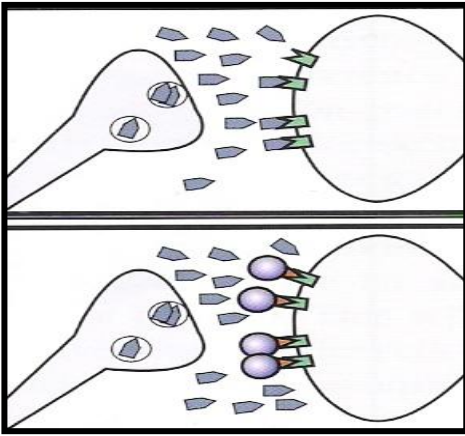


Figure 3: The Dopamine Receptor Antagonist Hypothesis of Antipsychotic Drug Action

Blockade of post synaptic dopamine receptors in the mesolimbic pathway is thought to mediate the efficacy of the drug and its ability to diminish positive symptoms.

Side effects: (Stahl,S, (1999) Psychopharmacology of Antipsychotics, Martin Dunitz, London).

Side effects: Antipsychotics –Common-

- Sedation
- Orthostatic hypotension
- Tachycardia
- Dry mouth
- Blurred vision
- Constipation
- Nausea
- Urinary retention
- Sexual adverse effects
- Extrapyramidal side effects
- Weight gain
- Hyperglycaemia
- Hyperprolactinaemia

Rare and Serious side effects –

- Neuroleptic malignant syndrome
- ECG Changes (broadened QT interval)
- Arrhythmias
- Cardiac arrest
- Sudden death
- Seizures

Atypical Antipsychotics

Individual drugs act as antagonists at different dopamine receptor subtypes. All except amisulpride act as serotonin receptor antagonists. They are sometimes known as serotonin-dopamine antagonists (SDAs). The action of serotonin-dopamine antagonism differentiates atypical anti-psychotics from the conventional drugs. Atypical drugs are generally better tolerated and have less EPSE than conventional anti psychotics. Clozapine is the only antipsychotic considered to be of superior efficacy, but because of its adverse effect profile, it should only be used for treatment resistant patients.

Atypical Antipsychotics available for use in Australia

- Quetiapine
- Risperidone
- Clozapine
- Olanzapine
- Amisulpride
- Aripiprazole
- Ziprasidone
- Paliperidone Extended Release

Indications

Schizophrenia and related psychosis
Acute mania

Physiological Action Atypical Antipsychotics

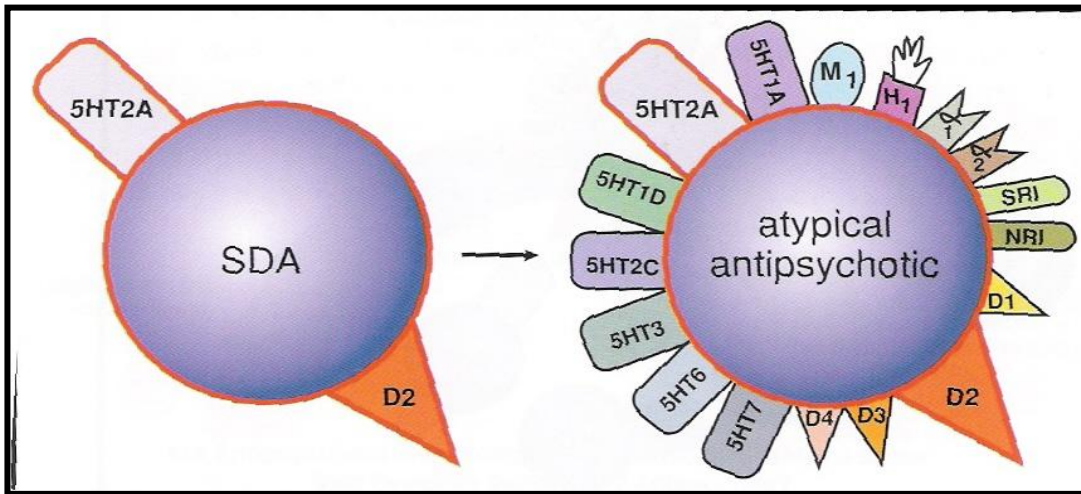


Figure 4: Atypical Antipsychotics

These drugs are not just simply serotonin-dopamine antagonists. They have very complex pharmacologic properties. These agents act on multiple dopamine and serotonin receptors and the noradrenergic and cholinergic system.

((Stahl,S,(1999) Psychopharmacology of antipsychotics, Martin Dunitz, London)

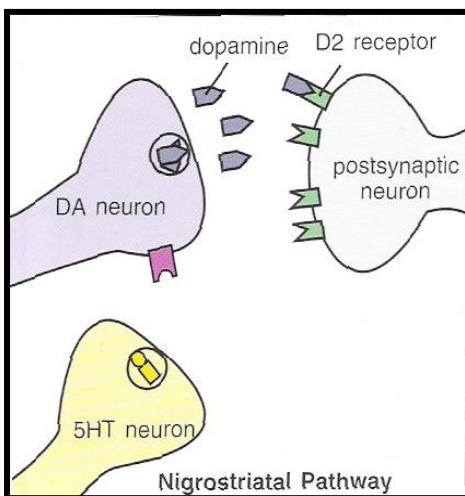


Figure 5: Serotonin and Dopamine Interactions

This pathway regulates movement. Dopamine release from this pathway is regulated by serotonin. Dopamine and serotonin have a reciprocal relationship. Here, no serotonin is present at the receptor, therefore dopamine is being released.

((Stahl,S, (1999) Psychopharmacology of antipsychotics, Martin Dunitz, London)

Side effects –atypical antipsychotics – common

- Sedation
- Dry mouth
- Constipation
- Dizziness
- Nausea
- Dose related EPSE (amisulpride, risperidone, paliperidone)
- Hypotension
- Weight gain (olanzapine, clozapine)
- Anxiety
- Agitation

- Hyperglycaemia (olanzapine, clozapine)
- Neutropenia (clozapine)

Rare and Serious side effects:

- Seizures
- QT prolongation
- Neuroleptic malignant syndrome
- Cardiomyopathy, myocarditis (clozapine)

Warning

Clozapine is used in people who have been previously unresponsive to other antipsychotics. Clozapine has a serious adverse effect profile and requires strict monitoring. There are strict guidelines relating to the commencement and ongoing monitoring of Clozapine.

Agranulocytosis: Because of a significant risk of agranulocytosis, a potentially life-threatening adverse reaction, reserve clozapine for use in the treatment of severely ill schizophrenic patients who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Consequently, before initiating treatment with clozapine, it is strongly recommended that a patient be given at least 2 trials, each with a different standard antipsychotic drug product, at an adequate dose and for an adequate duration.

Patients who are being treated with clozapine must have a baseline white blood cell (WBC) and differential count before initiation of treatment and regular WBC counts during treatment and for 4 weeks after the discontinuation of clozapine.

Clozapine is available only through a distribution system that ensures monitoring of WBC and neutrophil counts prior to delivery of the next supply of medication.

Seizures: Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Use caution when administering clozapine to patients having a history of seizures or other predisposing factors. Advise patients not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others.

Myocarditis: Clozapine may be associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. If myocarditis is suspected, promptly discontinue clozapine treatment.

Other adverse cardiovascular and respiratory effects: Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine, start treatment with 12.5 mg once or twice/day

Because collapse, respiratory arrest, and cardiac arrest during initial treatment have occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug (**Drug Facts & Comparisons Pocket Version, 2007 Edition**)

Antipsychotic Medications:

Side effects and management:

Sedation: Sedation is associated with all antipsychotics. It tends to be most pronounced at the initiation of therapy or with upward dose titration. Starting at low doses and titrating up the dose slowly can reduce the impact of sedation. Clients should be advised to expect sedation in the early stages of treatment, and that this may affect their ability to drive or operate machinery safely.

Postural hypotension: Some antipsychotics are associated with postural hypotension. and this may increase the risk of falls particularly in aged persons. Advice should be provided in accordance with each client's clinical presentation.

Anticholinergic effects: Most antipsychotic drugs possess some degree of anticholinergic activity (dry mouth, blurred vision, increased intraocular pressure, constipation and urinary hesitancy – older people may be more susceptible to delirium). The exceptions are: amisulpride, aripiprazole and risperidone.

Weight gain: Most antipsychotic medications cause weight gain. Clozapine, olanzapine and to a lesser extent quetiapine are associated with weight gain. Baseline Body Mass Index (BMI) and weight should be taken prior to commencing antipsychotic medications for monitoring throughout treatment.

Metabolic effects: Some antipsychotic medications are associated with abnormal glucose tolerance and increased serum lipids and place client at increased risk of diabetes, cardiovascular disease, risks that are augmented by obesity and lifestyle factors such as smoking and lack of exercise. It is recommended that fasting blood glucose and serum lipid measurements be measured around the onset of treatment in all cases and annually thereafter, but at least every 6 months in clients placed on clozapine or olanzapine. Counselling in regard to diet, exercise and smoking cessation/reduction are important.

Hyperprolactinemia: Raised prolactin may lead to gynaecomastia, galactorrhea, amenorrhoea, anovulation, impaired spermatogenesis, decreased libido, impaired sexual arousal, impotence and anorgasmia. These effects are dose dependent and associated with varying degrees with all antipsychotic drugs, with the possible exception of aripiprazole, clozapine and quetiapine. Routinely enquire about menstrual irregularities and sexual functioning.

Sexual dysfunction: Some antipsychotic medications can be associated with sexual dysfunction or sexual problems. Clinicians should ask questions early into treatment about sexual function.

QTc interval prolongation: Some antipsychotics may prolong the QTc interval which could lead to a life threatening condition called torsade de pointes. Thioridazine, pimozide, ziprasidone and droperidol are more likely to contribute to this condition. Women and people with hypokalemia, hypomagnesaemia, hypocalcaemia, renal failure, cardiac failure or a congenital disposition, are more susceptible to prolongation of the QTc interval. If a client's history or family history suggests susceptibility, an electrocardiogram (ECG) should be done before starting treatment and there must be regular monitoring during treatment.

Extrapyramidal side effects: These effects are generally an indication that the dose of drug has exceeded the optimal therapeutic range for a given patient and should be reviewed.

Acute dystonia's: Dystonia's tend to develop within hours to days of antipsychotic administration and affect the face, neck and trunk. Dystonia's such as an oculogyric crisis or opisthotonos can occur. Laryngeal spasm is also potentially fatal adverse effect. Young males are more susceptible to acute dystonia's than others. Dystonia's are treated with intramuscular antiparkinsonian (anticholinergic) medication such as benztropine.

CAUTION:

Acute Dystonia

Symptoms commonly occur secondary to neuroleptic medication. Generally develops within minutes to days and often affect the face, trunk, neck or hands. Less common with atypical antipsychotics.

Types of dystonia include:

- Laryngospasm (can cause death). Patient may complain of suffocation or be unable to speak (listen for stridor)
- Torticollis (head forced to one side)
- Retrocollis (head forced backwards)
- Protruding tongue with difficulty swallowing
- Opisthotonos (hyperextension of the back)
- Oculogyric crisis (eyes rolled upwards or laterally)

Intervention

This is a serious medical condition. Refer for medical assessment and treatment urgently. Provide appropriate education and information to the patient. Ensure adverse effects are documented in the clinical record.

Akathisia: is a severe sense of agitation restlessness which tends to be experienced in the limbs, especially the legs, It generally occurs within a few weeks of initiating treatment but can occasionally occur later in treatment. Consider a dose reduction or referral for medical review or switching to another antipsychotic medication.

Parkinsonism: Initially poverty of movement and rigidity may be seen and later tremor, drooling and hypersalivation may be evident. It is typically seen in the early weeks of treatment. Consider dose reduction or switching to another antipsychotic before using antiparkinsonian (anticholinergic) medication.

Tardive dyskinesia: Is a complex syndrome of involuntary hyperkinetic movements, usually large in amplitude, irregular, and worsened with distraction. It most frequently affects the mouth, lips, tongue and jaws, with smacking, tongue writhing, sucking or chewing movements and tic-like movements of the lips, eyes and facial muscles. The limbs and trunk can be affected with choreoathetoid movements. Anxiety increases the abnormal movements, which disappear in sleep. They can interfere with breathing, speaking and eating and are socially stigmatising. If detected early and if the antipsychotic medication can be reduced or ceased then tardive dyskinesia can often be fully reversible. Because of the lack of suitable management for established tardive dyskinesia, prevention is clearly preferred.

(Reference - Therapeutic Guidelines (2003) Psychotropic Therapeutic Guidelines Pty Ltd Version 5)

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome: All antipsychotics can cause this rare but potentially fatal adverse effect, which can develop at any time during treatment. It should be considered in any client who presents with high temperature, muscle rigidity, altered consciousness, autonomic instability and raised creatinine kinase. Other features can include neutrophilia and occasionally haemorrhagic tendency. If a client is suspected of or has neuroleptic malignant syndrome, they must attend the Emergency Department and have a review by a psychiatrist immediately.

Symptoms include hyperthermia, muscle rigidity, autonomic dysfunction and altered consciousness associated with antipsychotic medication. Signs are variable and may include tachycardia, tachypnoea, diaphoresis, labile BP, sialorrhoea, nausea or dysphagia. Sometimes the patient will not feel unwell. Not all symptoms may be present and a high degree of suspicion should be maintained for NMS. Onset is hours to days. Higher incidence in young men, high dose antipsychotics, recent commencement or increased dose of antipsychotics, typical antipsychotics and concurrent lithium use (can occur with atypical antipsychotics). Typically white cell count, creatine kinase (CK) and LFTs are raised (clinical manifestations can be variable). If there is uncertainty, admission to a general hospital for observation would be advised.

Therapeutic Guidelines (2003) Psychotropic Therapeutic Guidelines Pty Ltd Version 5

Intervention

This is a serious medical condition. Consult a senior Medical Officer or Psychiatrist urgently and refer the patient for treatment. This is a life threatening condition requiring urgent medical attention. Immediate management includes ceasing antipsychotic medication, cooling, renal, respiratory and cardiovascular support and monitoring for electrolyte imbalance.

Consult with a psychiatrist as soon as possible and arrange a review of medications. Provide appropriate advice, education and information to the patient regarding the condition.

Pregnancy

On the basis of limited available data, conventional or typical drugs appear to present no serious problems in pregnancy, with the possible exception of Chlorpromazine. There is evidence that this can cause a small increased risk of congenital abnormalities. However, large doses of any of these drugs can cause adverse effects in the neonate. Avoid if possible, or use the lowest effective dose. It should be noted that poorly controlled psychotic disorders may compromise maternal health and pregnancy outcomes. Neonatal adverse effects observed include generalised hypertonicity and dystonic reactions. The safety of atypical agents has yet to be established. On the basis of limited case report and studies there appears to be no deleterious effects to the foetus. There have been isolated cases of congenital abnormalities with the use of Clozapine. The most data available is for the use of olanzapine and no increased risk has emerged. The conventional agents are generally preferred. Supervised dose reduction and cessation 7-10 days prior to delivery should be considered.

Conclusion

Conventional and atypical antipsychotics are used as the foundation for the pharmacological management of schizophrenia and related psychosis. All antipsychotics are considered to be of equal efficacy, with the exception of Clozapine. The newer atypical agents are generally better tolerated and have less EPSE than the older conventional agents. Although the atypical agents have a broad adverse effect profile they are considered to be first line treatment in the management of psychotic disorders. Antipsychotics should be started at the lowest effective dose and titrated upwards and ongoing monitoring and management of adverse effects is required. Caution must be exercised with regards to the numerous drug interactions and the potential for neuroleptic malignant syndrome and other serious adverse effects.

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