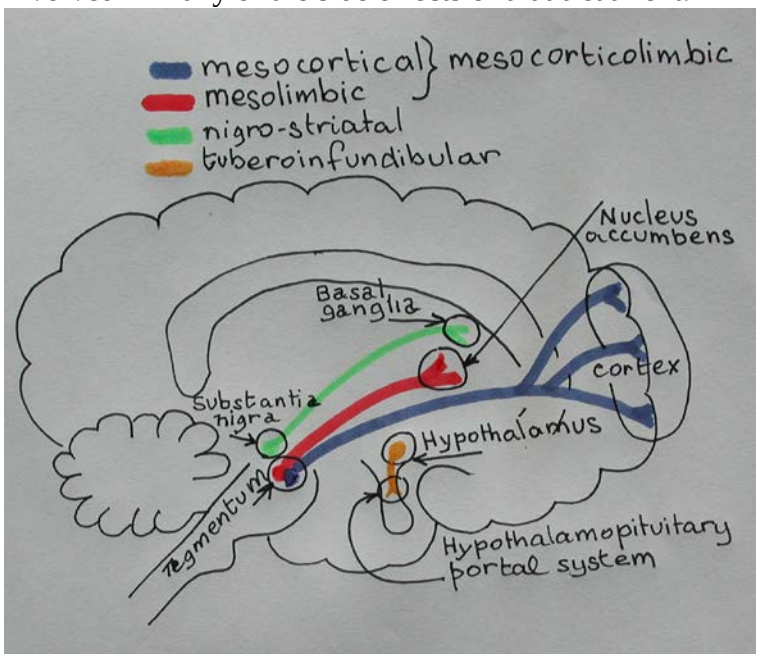
CHAPTER 15.

ANTIPSYCHOTIC DRUGS

Introductory summary of the dopamine pathways

The dopamine pathways are the focus of the drug treatment of psychosis, and are involved in many of the side effects of that treatment.



The dopamine pathways in the brain.

1) Dark blue: **mesocortical** pathway, extends from the ventral tegmental region of the mid-brain to the frontal cortex. One theory of schizophrenia poses that underactivity in this pathway causes an early event in the development of schizophrenia: difficulties with executive and other cognitive functions. Also, it is possible that underactivity of this pathway may be involved in the negative symptoms of schizophrenia. The side-effect of antipsychotics known as the "secondary" negative symptoms may arise in large part through further disruption of transmission in this pathway.

2) Red: **mesolimbic** pathway, extends from the ventral tegmentum to the nucleus accumbens, a limbic system structure. Impulses then pass on to other components of the limbic system and temporal lobe structures (including the auditory cortex). In the theory of schizophrenia mentioned in (1), when cognitive tasks are performed less efficiently, there is a compensatory increased activity in the mesolimbic pathway, and this increase produces the positive symptoms of hallucinations and delusions. The antipsychotics are directed at this pathway. As the limbic system is also involved in pleasurable sensations, this pathway may also be involved in negative symptoms.

3) Green: **nigrostriatal** pathway extends from the substantia nigra of the midbrain to the basal ganglia. Blockade of the nigrostriatal pathway by the antipsychotics is unintended and results in movement side-effects. To rebalance the extrapyramidal system, an acetylcholine blocker may be administered.

4) Yellow: **tuberoinfundibular** pathway extends from the hypothalamus to the portal system which serves the anterior pituitary. In the healthy individual, tonic release of dopamine into this system inhibits the release of prolactin. Unintentional disruption of this system leads to elevation of serum prolactin and the side-effects of gynecomastia, galactorrhea and sexual dysfunction.

The difficulties of classifying drugs

For convenience, psychiatric medications are classified according to the disorder for which they were initially or are most commonly marketed. However, particular psychiatric medications are often used for disorders outside their "classification". For example, the selective serotonin reuptake inhibitors (SSRIs) which were initially marketed as antidepressants, have become the drugs of first choice in most anxiety disorders and OCD, and the tricyclic antidepressants (TCAs) are used in bed-wetting (enuresis) because their anticholinergic "side-effects" cause tightening of the bladder neck.

The so-called "side-effects" of drugs may sometimes be useful, for example, people with major depressive episodes who have difficulty with sleep may benefit from an antidepressant with sedating "side-effects" being given at night.

Interestingly, LSD (lysergic acid diethylamide) and Ecstasy, now considered dangerous and illegal, have both been considered as potential psychiatric treatments.

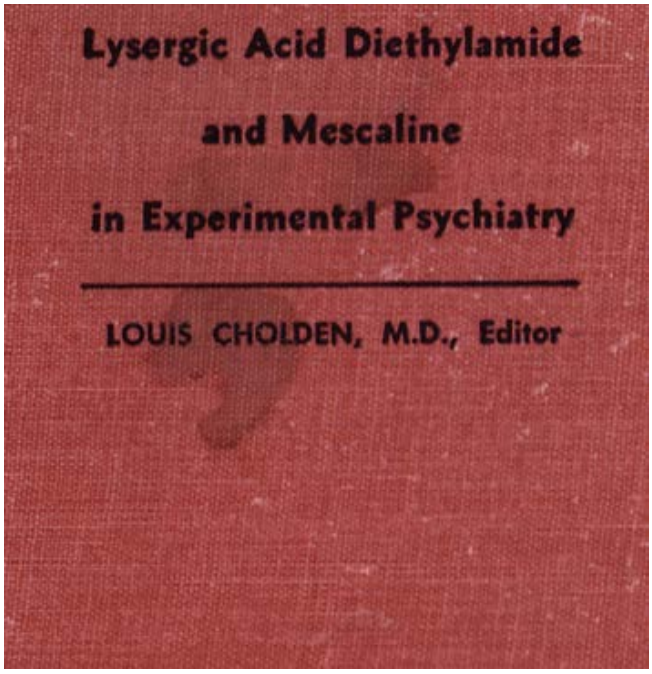


Illustration. "…and the dog will have his day." *Shakespeare (1564-1616)*

Introducing the antipsychotic drugs

The antipsychotic drugs (antipsychotics) are used in a range of conditions. They are the mainstay of the treatment of schizophrenia and will be discussed below in that context. However, they are also the mainstay of the management of delusional disorder, psychosis which occurs in dementia, they have a place in the management of delirium, and they must be added to antidepressants for the successful management of psychotic depression. The antipsychotics have a central place in the management of acute mania (even in the absence of delusions and hallucinations). Olanzapine, aripiprazole and others have gained acceptance as mood stabilizers (prophylactic

agents in mood disorders). Quetiapine has been approved by the FDA (USA) as a treatment for bipolar depression (Dando & Keating, 2006). In rare cases antipsychotics are used in the management of insomnia and anxiety (Carson et al, 2004), but this is not recommended and is best left to experts.

THE TYPICAL ANTIPSYCHOTICS

The typical antipsychotic drugs were the first effective antipsychotics. Chlorpromazine was the first, being described by French doctors in 1952. Others followed, including: haloperidol, fluphenazine and thiothixene. There is a straight line relationship between the affinity of the typical antipsychotics for the dopamine D2 receptor and the therapeutic dose of these agents used in acute schizophrenia. This is consistent with the dopamine hypothesis of schizophrenia

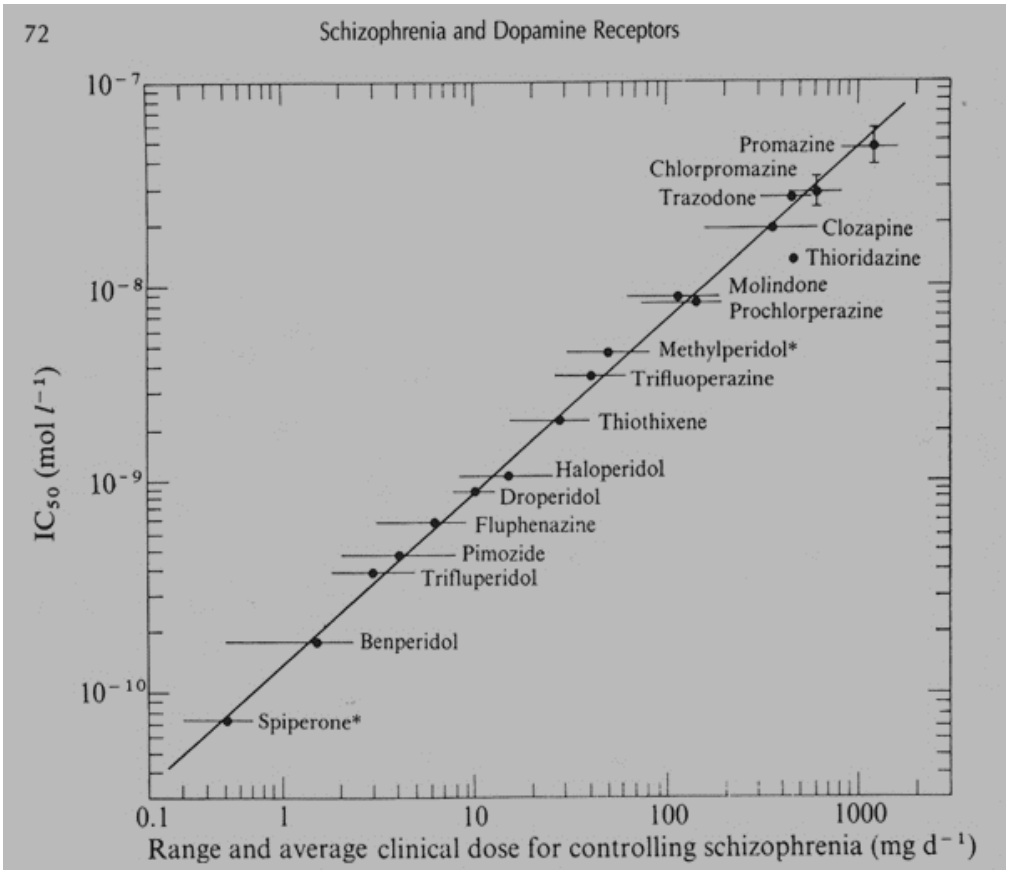


Illustration. Typical antipsychotics. Affinity for the dopamine D2 receptor (y-axis). Therapeutic doses (x-axis). This straight line relationship supports the dopamine hypothesis of schizophrenia.

Side-effects of typical antipsychotics

The extrapyramidal system (EPS) - the EPS is not a side-effect of antipsychotics, but needs to be mentioned before certain side effects. The EPS is a component of the motor system composed of dopamine (DA) and acetylcholine (Ach) neurons which enjoy a reciprocal/balanced relationship. In some individuals when DA receptors are blocked, the balance in the system is disrupted, leading to side-effects. This is particularly a feature of the older, First Generation Antipsychotics (FGAs).

Acute neurological side-effects (**acute EPS effects**) occur secondary to D2 receptor blockade in the EPS. These can appear on the first day of treatment and can take various forms of involuntary muscle spasm, particularly involving of the jaw, tongue, neck and eyes. A dramatic form is **oculogyric crisis** – in which the neck arches back and the eyes roll upward. A potentially dangerous form is **laryngospasm** – an early warning sign may be the patient's voice becoming higher pitched.

Balance has been disturbed resulting in muscle spasm, and can be restored by acute treatment with oral or intramuscular injection of an anti-Ach – such as benztropine (2 mg). The response is immediate and pleasing.

Medium-term neurological side-effects are also due to D2 blockade in the EPS.
Akathisia usually occurs in the first few day of treatment and involves either a mental and/or motor restlessness. Mental restlessness presents as increasing distress and agitation. Motor restlessness usually affects the lower limbs, with shifting from one foot to the other while standing and constant crossing and uncrossing of the legs while sitting. This is a difficult condition to manage. Useful steps include lowering the dose of the antipsychotic (if possible), adding diazepam or propranolol, or adding an anticholinergic (none of these is dramatically effective).
Parkinsonism usually occurs some days or weeks after the commencement of treatment. There is a mask-like face, rigidity of limbs, bradykinesia, and loss of upper limb-swing while walking. Tremor and festinating gait are less common. The best management is reduction in dose of the antipsychotic (if possible) and the addition of an anticholinergic agent.

Chronic neurological side-effects (**late EPS effects**) usually occur after months or years of continuous D2 blockade. **Tardive dyskinesia (TD)** manifests as continuous choreoathetoid movements of the mouth and tongue, frequently with lip-smacking, and may also involve the head, neck and trunk. Late EPS effects may continue after cessation of the typical antipsychotic.

Neuroleptic malignant syndrome (NMS) is probably due to disruption of dopaminergic function, but the mechanism is not understood. Untreated, the mortality rate is 20%, and immediate medical attention is mandatory. The symptoms include muscle rigidity, hyperthermia, autonomic instability and fluctuating consciousness. Renal failure secondary to rhabdomyolysis is a major complication and the cause of mortality.

Neuroendocrine effects result from blockade of dopamine transmission in the infundibular tract. Prolactin levels rise, with most antipsychotic agents and extreme cases may cause galactorrhea, amenorrhoea and infertility, and osteoporosis.

Anticholinergic side-effects include dry mouth, difficulty with micturition, constipation, blurred vision and ejaculatory failure. Anticholinergic delirium is a toxic confusional state; it usually occurs in patients taking a range of drugs directed at different symptoms, and antipsychotics may play a role.

Histamine blockade may produce severe sedation, and increased appetite.

Alpha adrenergic blockade may produce postural hypotension, cardiac arrhythmias and impotence.

Dermatological side-effects include skin rash and photosensitivity.

Weight gain is common with most antipsychotics.

Examples of typical/first generation antipsychotics (FGAs)

The oral forms of these medications are now uncommonly used.

Haloperidol produces EPS side-effects at high doses, but the oral preparation continues to be used in small doses (e.g., 0.5-1.0 mg bd) for brief periods for disturbed behavior in delirium and elderly patients. The IMI preparation (e.g., 10 mg) has a place in the management of younger disturbed people who are a danger to self or others (see later).

Zuclopenthixol continues to be used in two IMI preparations. **Zuclopenthixol acetate** (50-150 mg) is useful in the control of acute psychosis and disturbance. The beneficial effects last about 3 days. **Zuclopenthixol decanoate** (200-400 mg, 2-4/52) continues to command a small place in the long-term maintenance of chronic psychotic disorders.

THE ATYPICAL ANTIPSYCHOTICS

The term **"atypical"** cannot be defined, and should be replaced by, **"second generation antipsychotics"** (SGAs).

When these drugs first appeared they were called atypical because they were believed not produce EPS side-effects. However, experience has shown that they may produce these side-effects. But, they cause EPS symptoms far less commonly and less severely than the typical (first generation) antipsychotic agents.

The SGAs have a greater affinity than did the typical antipsychotics, for 5HT-2A receptors. They also have a greater affinity for 5HT-2A receptors than for D2 receptors.

A most important physiological feature is the interaction between serotonin and dopamine neurons in the basal ganglia. In this region (associated with movement) serotonin neurons inhibit the release of dopamine by dopamine neurons. Thus, **blockade of serotonin will increase the availability of dopamine** (thereby, reducing the rate of EPS side-effects).

Exceptions abound, however, and amisulpride, generally classed as an SGA has no affinity for serotonin receptors whatsoever.

Both FGAs and SGAs are effective in reducing the **positive symptoms** of schizophrenia (hallucinations, delusions and positive thought disorder).

The **negative symptoms** of schizophrenia include social withdrawal, self-neglect, loss of energy and drive, and poverty of thought. It has been construed that the negative symptoms are composed of two subgroups of symptoms: **primary** negative symptoms (being part of the illness process), and **secondary** negative symptoms (being apparent rather than actual symptoms of the disorder, instead, being secondary to drug treatment). Claims are made that the atypicals may produce no secondary negative symptoms, and go some way in relieving primary negative symptoms (Carpenter, 1996).

Other symptoms of schizophrenia include cognitive and mood difficulties and reduced quality of life. Evidence suggests that the atypical antipsychotics are helpful in all of these domains (Burton, 2006) than typical agents.

Structural brain changes associated with the disease process of schizophrenia have been identified. There is evidence that atypical antipsychotics (but not the typicals) ameliorate these changes. For example, the volumes of the thalamus and cortical grey matter increase with atypical antipsychotic treatment (Scherk & Falkai, 2006).

Side-effects of the SGAs

Most of the side effects of the FGAs can be encountered with the SGAs, however, they are less frequent and generally less severe.

Evidence suggests a decrease in life expectancy in people with schizophrenia of 10-20 years (Laursen et al, 2012). Multiple factors contribute including medication effects, poor general health care, smoking and sedentary life-style.

Weight gain is problem in schizophrenia and other mental disorders, in part, because of poor eating habits and lack of exercise. However, the antipsychotics exacerbate this problem and the metabolic syndrome. Weight gain, and metabolic syndrome exists in 10% of drug naïve people with schizophrenia (Mitchell et al, 2013).

A meta-analysis (Allison and Casey, 2001) estimated that over a 10 week period the mean increase was as follows:

1) clozapine 4.45 kg
2) olanzapine 4.15 kg
3) risperidone 2.1 kg (quetiapine probably similar)
4) ziprasidone 0.04 kg (aripiprazole probably similar).

The prevalence of **type 2 diabetes** in people with schizophrenia is double that of the general population. Over recent years there has been concern this is a direct result of antipsychotic treatment. As the SGAs are the most effective component in the medical management of psychotic disorders, this question has been soberly examined.

An association between schizophrenia and diabetes has been recognized for over a century. Risk factors for diabetes include poor overall health, lifestyle and level of access to heath care. Many SGAs are associated with weight gain, but there is no evidence for an intrinsic role for the antipsychotics in the aetiology of diabetes.

As this issue has been brought to the attention of clinicians, they have a responsibility to monitor the diabetes risk factors of patients (Poulin et al, 2005).

Hyperlipidemia (raised cholesterol and triglycerides) appears to be associated with the dibenzodiazepine-derived antipsychotics (clozapine, olanzapine and quetiapine).

QTc interval prolongation has been a matter of concern. The average QTc interval in healthy adults is about 400 msec, and a QTc interval of 500 msec or more is a risk factor for torsade de pointes (a ventricular arrhythmia which can lead to syncope, ventricular fibrillation and sudden death). One study found the following prolongations:

1) ziprasidone 20.3 ms
2) quetiapine 14.5 ms
3) risperidone 11.6 ms
4) olanzapine 6.8 ms
5) haloperidol 4.7 ms

Myocarditis and cardiomyopathy are rare (0.015-0.188 %; Merrill et al, 2005) side effects of clozapine therapy.

Recommendations for the monitoring/management of the side effects of the antipsychotics have been provided (Marder et al, 2004). However, further work is required.
When **weight gain** is anticipated (clozapine, olanzapine, quetiapine and risperidone) weight, height and BMI, along with abdominal girth at the umbilicus, should be recorded. Nutritional and life style (exercise) advice is recommended. With excessive weight gain a change to another agent may be considered. Metformin 750 mg daily can assist in weight reduction (Shulman et al, 2014).
When **diabetes** is anticipated (clozapine and olanzapine in particular) the weight is to be monitored and laboratory measures (eg fasting blood glucose) are indicated. When hyperlipidemia is anticipated (clozapine, olanzapine and quetiapine) serum cholesterol and triglycerides are to be monitored.
When **QTc prolongation** is anticipated (ziprasidone, particularly), ECG monitoring is recommended. In cases of increased cardiac risk (known heart disease, syncope, family history of early sudden death) special care, including regular ECT is recommended. **Myocarditis** has been associated with clozapine and clozapine clinics have specialized screening procedures.

Individual SGAs

As in all branches of medicine, if some disorders cannot be controlled with standard doses of a particular agent, first the dose is increased judiciously, and if the desired result remains evasive, another agent is trialled. The management of psychosis is difficult. Fortunately we have a range of atypical antipsychotics; while they have some similar actions, they come from a range chemical classes, and all have particular advantages. A series of trials may be necessary for the best possible outcome.

Clozapine

Clozapine is usually effective in treating schizophrenia which has been unresponsive to all other antipsychotics. However, it has a range of serious, potentially fatal side effects. Thus, clozapine is reserved for severe otherwise unresponsive psychosis, and must be managed by specialized clinics which conduct regular blood and other medical tests.

Clozapine is unique in causing neutropenia (potentially fatal) in 1-2% of patients. Other side-effects include significant weight gain, hypotension and tachycardia. Hypersalivation (unknown with the FGAs) can be troublesome with clozapine (and rarely with some other atypicals, such as olanzapine). 1% of patients experience seizures – this does not mean clozapine must be ceased – instead, anticonvulsants are added. This is a formidable array of side-effects, but the antipsychotic benefits are substantial. Clozapine is also useful in the treatment of TD.

Risperidone

Risperidone is an effective antipsychotic. At high doses (8 mg and above) it loses some of its advantages over FGAs, insofar, as acute EPS readily appear. A major disadvantage is the elevation of prolactin levels. A preparation which dissolves in the mouth is available. Risperidone has an advantage over some other SGAs as an IMI depot (long-acting) preparation is available. This can be administered once per fortnight during the maintenance phase, somewhat reducing compliance problems.

Paliperidone

Paliperidone is the active metabolite of risperidone, which was released when the patent of the parent chemical was about to expire. There is less weight gain, but more EPS problems, and the elevation of prolactin remains problematic. The dosing strategy is simpler, a single daily dose is possible.
Recently a paliperidone depot has become available which need only be repeated monthly (a great advantage over 2/52 injection). The monthly dose is usually 25-50 mg.

Olanzapine

Olanzapine is an effective antipsychotic which has gained acceptance as a mood stabilizer (used in the prophylaxis of mood disorder; Tohen et al, 2005). It has a pharmacological action and side-effect profile similar to clozapine (except, it is not associated with blood dyscrasia). The most troublesome side-effects are weight gain and sedation. The risks of diabetes and hyperlipidemia need to be monitored. An occasional side-effect, which is seen more regularly with clozapine, is hypersalivation. Olanzapine does not elevate prolactin to a significant degree. The sedating/calming effect of olanzapine is useful in acute disturbance. Olanzapine has an advantage of over some other SGAs in being available in an IMI form for acute

administration. A preparation which dissolves in the mouth is available. A long-acting depot form is available but because physiological response is variable, the patient must be observed for 3 hours following every injection (which is proving to be a disincentive).

Quetiapine

Quetiapine is an effective antipsychotic which has a receptor binding profile similar to clozapine, but with relatively lower affinity for all receptors. The side-effect profile is favourable, 75% of respondents denying any side-effects (Hellewell et al, 1999). Sedation and hypotension are reported, especially during the commencement phase. Weight gain, and the risk of diabetes and hyperlipidemia need to be considered. Quetiapine has little affinity for muscarinic receptors so that blurred vision and difficulty with micturition are rarely problems. The rate of EPS symptoms is similar to placebo and there is no significant elevation of prolactin.

Amisulpride

Amisulpride is a useful antipsychotic which has effects (potent antagonist) only at D2 and D3 receptors, and no effect on serotonin receptors. Thus, it could be considered an FGA, which was released in the age of the SGAs. At recommended doses it appears to be selective for limbic (rather than extra-pyramidal system) receptors (Xiberas et al, 2001). Unfortunately, when higher doses are required, EPS side-effects may become a problem. Amisulpride is less likely to cause weight gain than the other SGAs, but it produces robust elevation of prolactin levels, thus breast development and lactation in both men and women and amenorrhoea in women may be bothersome side effects (Leucht et al, 2013).
Some guidelines list amisulpride as benign with respect to QTc prolongation and sudden death (Hasan et al, 2012). It has low sedation effects, and discontinuation rate, suggesting it is well tolerated.

Aripiprazole

Aripiprazole is unusual - rather than an antagonist of dopamine receptors, it appears to be a high affinity partial agonist at presynaptic D2 receptors and an antagonist at postsynaptic D2 receptors. It has little affinity for D3, D4 and D1-like receptors, and its affinity for 5HT-2A receptors is low. There is some alph-1 blockade and orthostatic hypotension has been reported. The efficacy appears similar to risperidone and less than olanzapine, but the side-effect profile appears favourable at manufacturer recommended doses, with minimal elevation of prolactin (Komossa et al, 2009). However, a recent review demonstrated no clear advantage over many other SGAs (Khanna et al, 2013).

Aripiprazole has a role as a mood stabilizer (Keck et al, 2007).

Asenopine

Asenopine is unique in being administered sub-lingualy. It appears to be an effective antipsychotic (compared to the other available agents – but, none of them are much good). It has a lower profile of weight gain and adverse changes in glycemic or lipid profile (Bobo, 2013), which will be considered an advantage. It does not significantly increase prolactine (Leucht et al, 2013). However, dose related akathisia and oral hypoaesthesia, my be problematic.

Blonanserin, Iloperidone, Lurasidone, and Sertindole

Blonanserin has been released for use in Japan and Korea. It appears to be an effective anti-psychotic, which lowers the serum prolactin level (Kawabe et al, 2013. **Iloperidone** and **Lurasidone** have been released in the USA but their place in the clinical armamentarium remains to be determined.

The question has been raised (Leucht et al, 2013) – with the earlier SGAs coming off patent – will these newer SGAs be cost-effective (good value for money).

ACUTE AND LONGTERM ANTIPSYCHOTIC USE

Acute treatment is straightforward if the patient is able to cooperate and accepts oral medication. One of the SGAs should be commenced immediately and raised to the generally agreed therapeutic level over a few days. Preparations which are absorbed in the mouth, and don't require the act of swallowing (olanzapine, risperidone and asenapine) can be very useful in the early stages. Dosage needs to be tailored to the particular patient. Initially, a regular small amount of a benzodiazepine may help with distress and insomnia.

When the patient is unable to cooperate and represents a danger to self or others, it may be necessary to administer medication against the patient's wishes. No action should be taken until sufficient personnel are available – the last thing we want is a fight. At least 5 (preferably) people are necessary to humanely administer medication against the wishes of the disturbed patient. Four people over-power ("take-down") the patient, while a fifth (preferably with a trained assistant) administers the medication. The action is planned. One method is for each of the "take-down team" to be designated a limb to inactivate. After the patient has refused to accept medication he/she is approached by the organized group. Again, the patient is asked to accept treatment and gently but firmly assured that if he/she does not accept treatment, for his/her benefit, the medication will be administered without his/her cooperation. When faced with the inevitable, many reluctant patients will eventually comply.

Should co-operation prove impossible, when there is a threat to the safety of the patient or others, the group should move together to place the patient in the prone position. This may be on a treatment trolley; while perhaps less "dignified" it is safer for many reasons, to immobilize the patient on the floor. With one person designated to each limb, and acting together, there is little risk to the staff. Once the patient is in the prone position with weight applied over the pelvis, the staff are in control of the situation.

Each treatment centre has a drug protocol for take-downs; drugs will be administered either IMI or IV. At some centres IMI midazolam 5mg (a benzodiazepine) and an IMI antipsychotic (haloperidol 10 mg, for example) are administered simultaneously. The midazolam should be effective within minutes, but will be metabolized with in 2 hours. The antipsychotic will take half an hour to achieve the desired effect, but will then be effective for 6-10 hours.

Until recently midazolam was administered with olanzapine, however, there were reports of this combination causing respiratory depression, and the practice has essentially ceased.

Another option is to forgo the immediate benefit of midazolam and use the IMI olanzapine alone.

Downward pressure (adequate but not excessive) should be maintained until there is evidence that the patient is calm and mildly sedated. This may not take as long as the pharmacology textbooks indicate, as once the medication has been given the patient may realise that further struggle is futile. If the desired effect is not obtained, oral or IMI olanzapine 10 mg can be repeated at 45 minute intervals until good control is established (to a maximum of 60 mg per day). Experience indicates that when control is difficult obtain, it is useful to regularly add a benzodiazepine to the antipsychotic, as these have different actions and there is a synergistic effect.

If the patient is well known and has remained uncooperative and violent for long periods previously, the typical antipsychotic zuclopenthixol acetate (Clopixol-Acuphase) may be administered IMI at the initial “take down”. This is a calming antipsychotic which is active for about 3 days.

Long-term treatment may be oral or IMI. If the patient has good insight and well organized, maintenance with an oral atypical antipsychotic is indicated. If this is not the case, a fortnightly IMI of an atypical antipsychotic may be indicated, such as risperidone 25-50 mg (Resperdal Consta). Long acting paliperidone (Xeplion) 25-50 mg need only be repeated monthly. The FGA, zuclopenthixol decanoate (200mg) is an effective alternative.

An olanzapine long lasting IMI preparation (Zyprexa Relprvv) is available (210-405 mg). It may be given monthly and has some advantages. However, regulations about supervising patients for 3 hours post each injection is inconvenient, and some services have developed special clinics for the purpose.

The period of time for which treatment continues will depend on the disorder and response to treatment. In the initial stages of schizophrenia it is best to advise that treatment will be necessary for at least 6 months, probably a year, before this question can be properly addressed. In many psychotic disorders, indefinite medication is indicated, but the patient may not accept this advice while lacking insight.

References

Allison D, Casey D. Antipsychotic-induced weight gain: a review of the literature. Journal of Clinical Psychiatry 2001; 62(Suppl 7):22-31.
Bobo W. Asenapine, iloperidone and lurasidone: critical appraisal of the most recently approve pharmacotherapies for schizophrenia in adults. Expert Rev Clin Pharmacol 2013; 6:61-91.
Burton S. Symptom domains of schizophrenia: the role of atypical antipsychotic agents. Psychopharmacology 2006; 20 Supplement: 6-19.
Carpenter w. Maintenance therapy of persons with schizophrenia. Journal of Clinical Psychiatry 1996; 57 [Suppl. 9]:10-18.
Carson W, Kitagawa H, Nemeroff C. Drug development for anxiety disorders: new roles for atypical antipsychotics. Psychopharmacology Bulletin 2004; 38 Suppl 1:38-45.
Dando T, Keating G. Spotlight on quetiapine in acute mania and depression associated with bipolar disorder. CNS Drugs 2006; 20:429-431.
Hasan A, Falkai P, Wobrock T et al. Guidelines for treatment of schizophrenia. Wold J Biol Psychiatry 2012; 13: 318-378.
Hellewell J, Kalali A, Langham S, McKellar J, Awad A. Patient satisfaction and acceptability of long-term treatment with quetiapine International Journal of Psychiatry Clinical Practice 1999; 3:105-113.
Kawabe K, Horiuchi F, Ueno S. Blonaserin, a novel antipsychotic, is suitable for treating schizophrenia associated with hyperprolactinemia. Clin Neuropharmacol 2013; 36: 239-241.
Khanna P, Komossa K, Rummel-Kluge C, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2013 Feb28; 2:CD006569.
Keck P, Calabrese J, McIntyre R, et al. Aripiprazole mono therapy for maintenance therapy in bipolar I disorder: a 100 week, double-blind study versus placebo. Journal of Clinical Psychiatry 2007; 68:1480-1491.
Komossa K, Rummd-Kluge C, Schmid F, et al. Aripiprazole versus other antipsychotics for schizophrenia. Cochrane database Syst Rev 2009, Oct 7; (4):CD006569.
Laursen T Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr Opin Psychiatry 2012; 25: 83-88.
Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet2013; 382: 951-962.
Marder S, Essok S, Miller A, et al. Physical health monitoring of patients with schizophrenia. American Journal of Psychiatry 2004; 161:1344-1349.
Merrill D, Dec G, Goff D. Adverse cardiac effects associated with clozapine. Journal of Clinical Psychopharmacology 2005; 25:32-41.
Mitchell A, Vancampfort D, De Herdt A, et al. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia. Schizophrenia Bulletin 2013; 39: 295-305.
Poulin M-J et al, Atypical antipsychotics in psychiatric practice: practical implications for clinical monitoring. Canadian Journal of Psychiatry 2005: 50:555-562.
Scherk H, Falkai P. Effects of antipsychotics on brain structure. Current Opinion in Psychiatry 2006: 19:145-150.

Schulman M, Miller A, Misher J, Tentler A. Managing cardiovascular disease risk in patients treated with antipsychotics. Journal of Multidisciplinary Healthcare 2014; 7: 489-501.
Tohen M, Greil W, Calabrese J. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12 month randomized double-blind controlled clinical trial. American Journal of psychiatry 2005; 162:1281-1290.
Xiberas X, Martinot J, Mallet L. In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. Journal of Clinical Psychopharmacology 2001; 21:207.