Pridmore S. Download of Psychiatry, Chapter 15. Last modified: February, 2018.

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CHAPTER 15.

ANTIPSYCHOTIC DRUGS

This sounds a bit complicated. Don't worry. There are two main groups, the first generation antipsychotics (FGAs) and the second generation antipsychotics (SGAs). There are two main sets of side-effects – extrapyramidal system side-effects (EPSs) and Metabolic syndrome (MetS) symptoms. There are oral and intramuscular preparations.

Probably the greatest use of the antipsychotics is in schizophrenia. However, they are also used in bipolar disorder, delirium, delusional disorder and some other circumstances.

The leading theory about the cause of schizophrenia is the 'dopamine hypothesis' – this states that schizophrenia is caused by overactivity of dopamine neurons (excessive release of dopamine). Thus, our current therapeutic efforts use agents which block dopamine receptors. But, naturally, in the process, some dopamine receptors which we would prefer not to block, get blocked – this is the cause of some unwanted effects.

The following few paragraphs attempt to give some facts about dopamine neurons and response to antipsychotics – this might be a bit boring to some, and can be skipped.

The dopamine pathways and schizophrenia
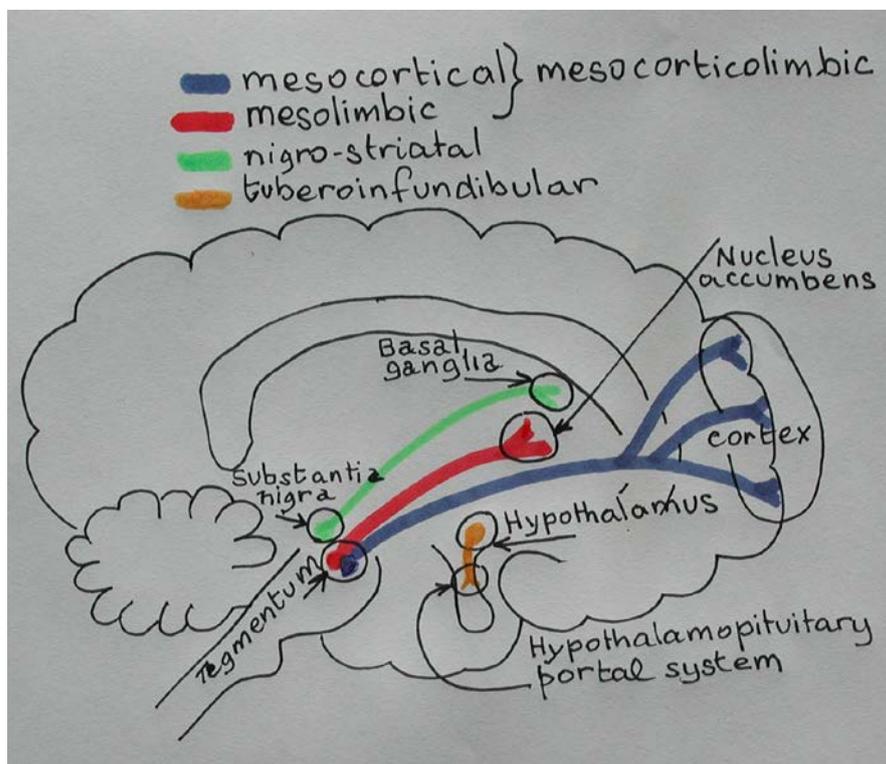
There are 4 dopamine pathways in the brain – these are briefly discussed below.

1. Blue: The **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 is an early event in the development of schizophrenia – it results in difficulties with executive and other cognitive functions. Also, it is possible that underactivity of this pathway is involved in the negative symptoms of schizophrenia. Those side-effect of the antipsychotics known as the, "secondary" negative symptoms, are thought to be due to the further (drug-induced) disruption of this pathway.

2) Red: The **mesolimbic** pathway, extends from the ventral tegmentum to the nucleus accumbens - a limbic system structure. From the accumbens, impulses then pass to other components of the limbic system and temporal lobe structures (including the auditory cortex). In the theory of schizophrenia mentioned in (1) above, when cognitive tasks are performed less efficiently (because the mesocortical pathway is underactive), there is a compensatory increase in the 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, decreasing activity in this pathway may also be involved in "secondary" negative symptoms (such as, loss of the ability to experience pleasure).

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

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

FIRST GENERATION ANTIPSYCHOTICS (FGA)

Until the mid-20 Century there was no useful treatment for psychosis. Chlorpromazine was the first of the FGAs – it was described by French doctors in 1952 – and arose from attempts to refine anti-histamine medications. Other antipsychotics followed, including, haloperidol, fluphenazine and thiothixene. There is a straight line relationship between the affinity of the FGAs for the dopamine D2 receptor, and the necessary therapeutic doses of these agents (see Illustration). This is consistent with, and contributed to, the dopamine hypothesis of schizophrenia.
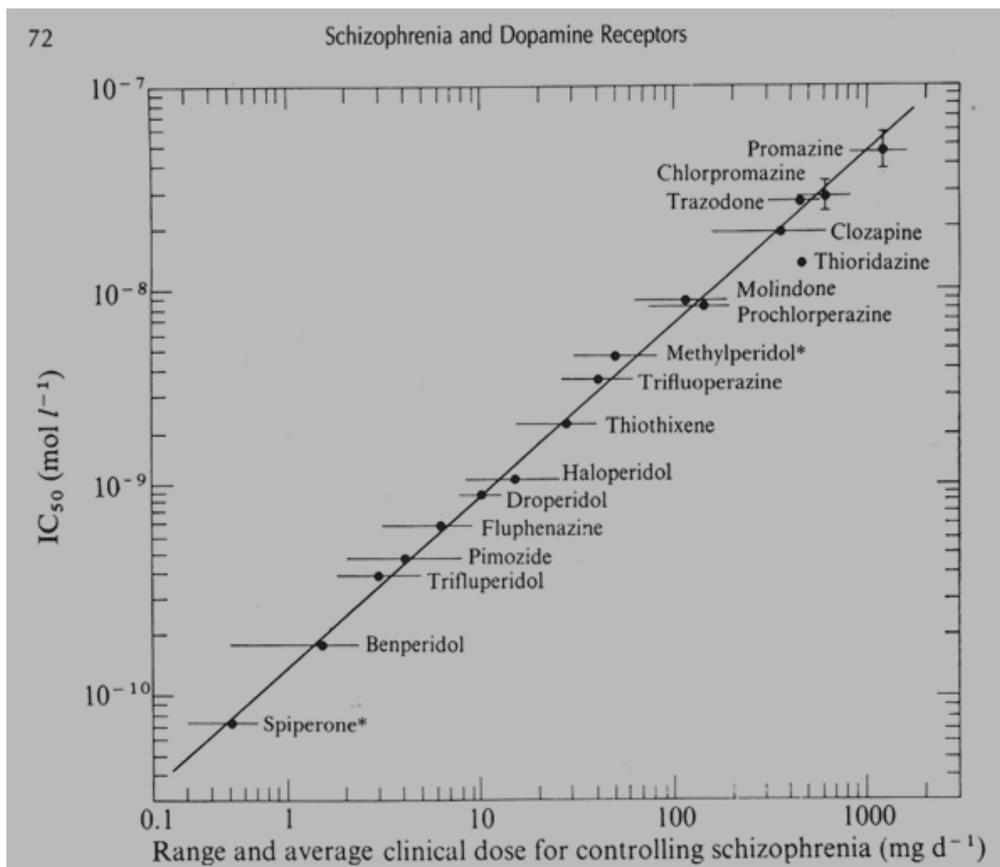
Illustration. FGAs. Affinity for the dopamine D2 receptor (y-axis) vs. Therapeutic doses (x-axis). This straight line relationship supports the dopamine hypothesis of schizophrenia.

Clinical use

FGAs are effective in reducing the **positive symptoms** of psychosis (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, not symptoms of the disorder, and instead, secondary to drug treatment). FGAs are said to cause secondary negative symptoms.

Side-effects of FGAs

Movement problems
Movement problems are the most characteristic side-effects of the FGAs.

First, we need to remember the **extrapyramidal system (EPS)** - a component of the motor system, which functions to facilitate smooth movement. It (the EPS) is composed to two, balanced pathways, one employing dopamine (DA) and the other, acetylcholine (Ach) releasing neurons. (The nigrostriatal pathway, a component of the EPS, is mentioned in **3) Green**, above.)

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

2. Medium-term EPS symptoms, also due to D2 blockade in the EPS.

Akathisia usually occurs in the first few days 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 (unfortunately, none of these is dramatically effective).

Parkinsonism usually occurs some days or weeks after 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.

3. Late EPS symptoms 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. TD may continue after cessation of the antipsychotic and has been considered untreatable. (However, deuterium tetrabenazine has recently emerged as a potential treatment. Cummings et al, 2018).

Neuroleptic malignant syndrome (NMS)
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 recommended. 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
The 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
The 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 contribute.

Histamine blockade
Histamine blockade produces sedation, and increased appetite.

Alpha adrenergic blockade
Produce postural hypotension, cardiac arrhythmias and impotence.

Dermatological side-effects include skin rash and photosensitivity.

Weight gain is common with most antipsychotics.

Examples of FGAs

The oral forms of these medications are no longer commonly 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 behaviour in delirium of elderly patients. An IMI preparation (e.g., 10 mg) for acute use 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.

SECOND GENERATION ANTIPSYCHOTICS (SGAs)

The SGAs have a greater affinity than the FGAs, for 5HT-2A receptors, and a greater affinity for 5HT-2A receptors, than for D2 receptors.

An important physiological feature - 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 increases the availability of dopamine** - thereby, reducing the risk of EPS side-effects.

[When the SGAs first began to appear, the FGAs were call "Typical" and the SGAs were called the "Atypical" antipsychotics. This was because - it was thought that movement problems were 'typical' of antipsychotic treatment, and as the SGAs were believe not produce movement problems, they were called, 'atypical'.]

As it happens, the belief that SGAs do not cause movement problems was very wrong (Divac N, et al. 2014). Acute EPS symptoms and tardive dyskinesia occur, but less commonly with the SGAs. Akathisia occurs equally in the FGAs and SGAs. Divac et al (2014) concludes, "These drugs have not lived up to the expectations regarding their tolerability".

Clinical use

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

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 have been made that the SGAs produce no secondary negative symptoms, and go some way in relieving primary negative symptoms (Carpenter, 1996).

SGAs (olanzapine, quetiapine, risperidone) present no danger to the foetus (Jayashri et al, 2015).

Side-effects of the SGAs

Movement disorders
It has been repeatedly stated that, initially, the SGAs were thought not to produce movement disorders. But, time has shown this is not correct – that acute EPS symptoms and tardive dyskinesia occur, but are less common in SGAs, and that akathisia occurs at about equal rates in FGAs and SGAs.

Reduced life expectancy
Evidence indicates 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 a sedentary life-style.

The metabolic syndrome
The metabolic syndrome is associated with the risk of developing cardiovascular disease and type 2-diabetes, and thus, mortality. It is diagnosed by the presence of three of the following: 1) abdominal obesity, 2) high blood pressure, 3) high blood sugar, 4) high serum triglycerides, and 4) low high-density lipoprotein (HDL).

Metabolic syndrome is more common in people with schizophrenia than the general population. It is more common in chronic than first episode schizophrenia. An important question, therefore, is whether the increased rate of metabolic syndrome in people with schizophrenia is a result of medication [particularly the second generation antipsychotics] - or whether it is associated with the disorder itself [conceivably it could be linked to the chemical process which cause schizophrenia; alternatively, it could be linked to behavioural changes which are features of the disorder – for example, negative symptoms and loss of drive may lead to reduced activity, leading in turn, to weight gain, etc.].

To this point, the side effects of antipsychotic medication seem to be the most important factor. The link between untreated schizophrenia (people at very high risk) and the metabolic syndrome is weak (Cordes et al, 2017).

Weight gain
Weight gain, and metabolic syndrome exists in 10% of drug naïve people with schizophrenia (Mitchell et al, 2013). This is likely, in part, a consequence of poor eating habits and lack of exercise, however, the antipsychotics exacerbate the problem.
 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).

Type 2 diabetes
The prevalence of **type 2 diabetes** in people with schizophrenia is double that of the general population. There is 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 health 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.

QTc interval prolongation
QTc interval prolongation is a matter of concern. The average QTc interval in healthy adults is about 400 msec - a QTc interval of 500 msec 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
Rare (0.015-0.188 %; Merrill et al, 2005) side effects of clozapine therapy.

Recommendations for the monitoring/management of side effects
Recommendations for the monitoring/management of side effects have been made –
but, they are complex, vary from centre to centre and are inconsistently applied.

These include, for weight gain – recording and review of weight, height, BMI, along
with abdominal girth at the umbilicus. 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 - weight is to be monitored and laboratory measures (eg
fasting blood glucose) are indicated. When hyperlipidemia is anticipated, 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 ECG is
recommended. **Myocarditis** has been associated with clozapine, and clozapine clinics
have specialized screening procedures.

Individual SGAs

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 SGAs, 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. An IMI depot (long-acting) preparation is available, which can
administered once per fortnight or less frequently, and potentially reduce 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.
Recently a paliperidone depot has become available which need only be repeated monthly (an 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 risk factors for diabetes and hyperlipidaemia 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. It 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. It has also been approved by the FDA (USA) as a treatment for bipolar depression (Dando & Keating, 2006).
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 hyperlipidaemia 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 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 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-lingual. It appears to be an effective antipsychotic (compared to the other available agents – but, none of them are much good). It has a lower weight gain and adverse changes in glycaemic or lipid profile (Bobo, 2013), which will be considered an advantage. It does not significantly increase prolactin (Leucht et al, 2013). However, dose related akathisia and oral hypoaesthesia, may 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.

ACUTE AND LONGTERM ANTIPSYCHOTIC USE

Acute treatment
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 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, 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 within 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
Long-term treatment may be oral or IMI. If the patient has good insight and is well organized, maintenance with an oral SGA is indicated.

If this is not the case, a long acting IMI SGA may be indicated. Alternatives include fortnightly risperidone 25-50 mg (Resperdal Consta) or monthly paliperidone 25-50 mg (Xeplion). Another SGA long acting preparations is aripiprazole lauroxil, which can be repeated at 6 weekly intervals – it is essentially free of prolactin elevation or significant metabolic side effects.

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 are inconvenient, and some services have developed special clinics for the purpose.

There is little evidence of any efficacy difference between these suggestions.

Three-monthly paliperidone palitate (3MPP) – has recently been described (Miyamoto and Fleischhacker, 2017).

NEGATIVE SYMPTOM TREATMENT

The negative symptoms of schizophrenia (e.g., loss of drive, and ability to experience and communicate pleasure), while not as dramatic as delusions and hallucinations, have a profound influence on outcome. There has been no pharmacological treatment.

MIN-101 is a compound with affinities for sigma-2 and $5-HT_{2A}$ receptors and no direct dopamine affinities. In a recent study (Davidson et al, 2017) it was found to significantly reduce negative symptoms. If MIN-101 proves to be useful in this way, it will be the greatest advance in schizophrenia treatment is the clinical life (>40 years) of the current author.

The study described looked at patients who had been clinically stable for 3 months. Their antipsychotics were withdrawn over 5 days and MIN-101 was then commenced. A problem which will need to be examined is whether the withdrawal of antipsychotics leads to relapse into psychosis, or perhaps MIN-101 has some antipsychotic action – we look forward to the next instalment.

IMMUNOLOGICAL THEROY OF SCHIZOPHRENIA

An immunological theory of schizophrenia (Beumer et al, 2012) – suggests inti-inflammatory drugs (including minocycline) may have a role in treatment. But, progress has been slow (De Picker et al, 2017).

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