

**ABSTRACT**

**Antipsychotics are a pharmacologically heterogeneous group of compounds, but all act as D2 dopamine receptor antagonists, an action linked to their antipsychotic effect. Today, sixty years on since 1952, we have the FGAs and the SGAs. These medications continue to be useful, and continue to have some troubling adverse effects. As a class, the FGAs are more likely to be associated with EPS but this is primarily true of medications that bind tightly with D2 neuroreceptors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine. Anticholinergic effects are especially prominent with weaker-binding FGAs, as well as with the SGA clozapine. As a class, the SGAs, especially clozapine and olanzapine generally tend to cause more problems relating to the metabolic syndrome, such as obesity and type 2 diabetes mellitus. All antipsychotic medications are associated with an increased likelihood of sedation, sexual dysfunction, postural hypotension, prolonged QT interval and sudden death. Primary care physicians need to be familiar with the individual adverse effect profiles of these medications.**

**Keywords: Antipsychotics, heterogeneous, dopamine receptor antagonists. First generation antipsychotics, second generation antipsychotics, extra-pyramidal symptoms, metabolic syndrome.**

**SFP2013; 39(1): 26-34**

**INTRODUCTION**

The antipsychotics are the only class of drugs for which the evidence base shows consistent efficacy in treating the core symptoms of schizophrenia and schizophrenia-like illnesses (Mackin & Thomas, 2011)<sup>1</sup>. Antipsychotics are a pharmacologically heterogeneous group of compounds, but all act as D2 dopamine receptor antagonists, an action linked to their antipsychotic effect (Agid et al, 2007)<sup>2</sup>.

Historically, two generations of antipsychotics are recognised. The “typical” (first generation) antipsychotic drugs (e.g. haloperidol, chlorpromazine, and trifluoperazine) have been used to treat schizophrenia since the 1950s. The “atypical” (second generation) antipsychotic drugs (e.g. risperidone, olanzapine, and clozapine) were introduced into routine practice from the 1990s. Both classes are used in the acute phase of schizophrenia and related psychoses and for long term maintenance and prevention of relapse. Choosing the most appropriate drug and

formulation for an individual may be more important than choosing the drug group.

This study unit updates the reader on several aspects of the medications in schizophrenia: treatment goals, mechanism of action of the antipsychotics, the typical antipsychotic drugs (FGAs) and atypical antipsychotic drugs (SGAs), adverse effects of antipsychotics, antipsychotic induced weight gain, and the use of antipsychotic medications in the different phases of schizophrenia.

**CHANGES IN TREATMENT GOALS FOR SCHIZOPHRENIA**

Figure 1 shows the changes in treatment goals for schizophrenia over the past decades as its psychopharmacology became better understood. Today, the goal of treatment is a good functional outcome targeted at remission and recovery.

Prior to the 1950s, treatment of psychotic disorders involved primarily institutional and supportive interventions, without effective treatment for the symptoms of these illnesses. (Hudepohl & Nasrallah, 2012).

In 1952, the arrival of the first antipsychotic medication chlorpromazine and with the initial success of this drug and other first generation antipsychotic medications effectively reduced the intensity of positive psychotic symptoms of hallucinations and delusions, allowing most institutionalised patients with schizophrenia to be discharged into community treatment. All in all, 51 neuroleptics from six chemical classes were developed; 12 are currently available in the USA (Hudepohl & Nasrallah, 2012; Nasrallah and Tandon, 2009)<sup>3,4</sup>. These are referred to as “first generation”, “classic”, “conventional”, or “typical antipsychotics. Although useful in dealing with the positive psychotic symptoms, the first generation antipsychotics (FGAs) had a range of adverse effects, notably extrapyramidal symptoms (EPS) such as dystonia, parkinsonism, akathisia, and tardive dyskinesia.

In 1959, clozapine was introduced as the first antipsychotic drug synthesised without any risk of EPS, which led it to being labelled as an “atypical”. It was initially marketed in Europe in 1972, but was withdrawn from the market in 1974 due to reports of many fatalities related to agranulocytosis. In 1989, clozapine was reintroduced in the USA after controlled studies showed efficacy in treatment-refractory patients with persistent delusions and hallucinations who had failed to respond to several FGAs. Weekly leukocyte monitoring was made a requirement for treatment, although less than 1% incidence was observed. (Hudepohl & Nasrallah, 2012)<sup>3</sup>.

Following the approval of clozapine, other “atypical antipsychotics” were developed and approved by the Food and Drug Administration (FDA) which had lower levels of EPS and somewhat broader efficacy on mood and negative

---

ROGER HO CHUN MAN, Consultant and Assistant Professor, Department of Psychological Medicine, National University Health Systems

symptoms, mimicking the effects of clozapine without the risk of agranocytosis. (Hudepohl & Nasrallah, 2012)<sup>3</sup>

Today, sixty years on since 1952, we have the FGAs and the SGAs. These medications continue to be useful, and continue to have some troubling adverse effects. With a better understanding of these side effects, we are able to optimise the use of these medications despite the troubling side effects to achieve remission and recovery with better functional outcomes.

**FIGURE 1. CHANGES IN TREATMENT GOALS FOR SCHIZOPHRENIA OVER THE PAST DECADES**

1952	<ul style="list-style-type: none"> <li>Reduction of (positive) psychotic symptoms – introduction of chlorpromazine</li> <li>Long-term treatment</li> </ul>
1980	<ul style="list-style-type: none"> <li>Negative symptoms</li> </ul>
1990	<ul style="list-style-type: none"> <li>Neuropsychological deficits</li> <li>Health-Related Quality of Life (HRQoL)/functional deficits</li> </ul>
2000	<ul style="list-style-type: none"> <li>Subjective well-being (SW)</li> <li>Early detection/delay of transition to psychosis</li> </ul>
2005	<ul style="list-style-type: none"> <li>Remission/recovery (functional outcome)</li> </ul>

## DOPAMINERGIC RECEPTOR BLOCKING IN THE MAJOR DOPAMINE PATHWAYS

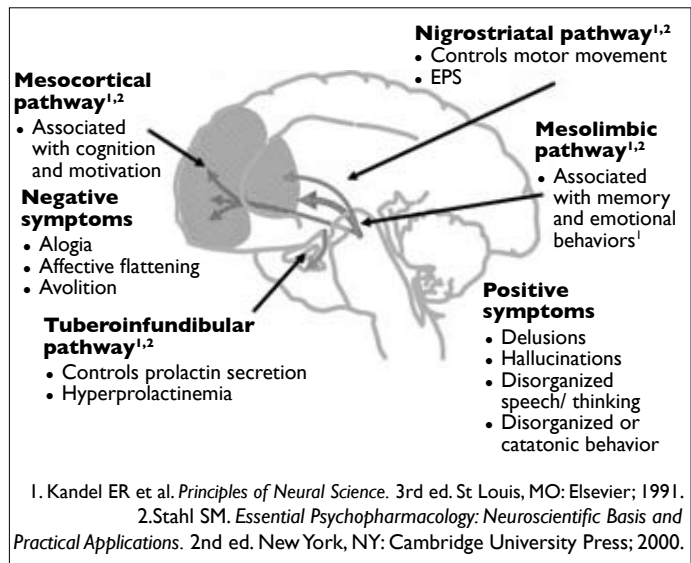
**The dopamine hypothesis.** The dopamine hypothesis of schizophrenia is currently used to explain the positive and negative symptoms of the disease. The postulate is that overactive mesolimbic dopamine (DA) neurons cause the positive symptoms of psychosis and the corollary that underactive mesocortical DA neurons, cause the negative, cognitive, and affective symptoms of schizophrenia.

The dopamine pathways are neural pathways in the brain which transmit the neurotransmitter dopamine from one region of the brain to another. There are 8 dopamine pathways in the brain, of which the four major ones are described below. See Figure 2.

**Mesolimbic pathway** – The mesolimbic pathway transmits dopamine from the ventral tegmental area (VTA) to the limbic system via the nucleus accumbens. The VTA is located in the midbrain and the nucleus accumbens is in the ventral striatum. Positive symptoms of schizophrenia (namely, delusions, and hallucinations) are believed to be the result of dopaminergic hyperactivity in the mesolimbic pathway of the brain. FGAs are antagonists at postsynaptic D2 receptors, and these treat the positive symptoms of schizophrenia by reducing dopaminergic activity. (Hudepohl & Nasrallah, 2012)<sup>3</sup>.

**Mesocortical pathway** – The mesocortical pathway transmits dopamine from the VTA to the frontal cortex. FGAs also block D2 receptors in the mesocortical pathways, which can worsen the cognitive and negative symptoms of schizophrenia. FGAs bind to D2 receptors tightly and for long periods of time, which can lead to an increase in adverse effects (Hudepohl & Nasrallah, 2012)<sup>3</sup>.

**FIGURE 2. MAJOR DOPAMINE PATHWAYS**



**Nigrostriatal pathway** – The nigrostriatal pathway transmits dopamine from the substantia nigra to the striatum. This pathway is associated with motor control. Deficiency of dopamine production in the substantia nigra results in Parkinson's disease.

**Tuberoinfundibular pathway** – The tuberoinfundibular pathway transmits dopamine from the hypothalamus to the pituitary gland. In the tuberoinfundibular pathway from the hypothalamus to the pituitary gland, prolactin is under tonic inhibition of dopamine. D2 blockade results in decreased dopamine tone, thereby increasing the secretion of prolactin. While this state is normal during the postpartum period, it can lead to adverse effects in some patients treated with a FGA with high potency D2 neuroreceptor blockade e.g. fluphenazine, haloperidol, thiothixene, and trifluoroperazine. Resperidone, which is the only SGA with prominent D2 blockade of this pathway, also has hyperprolactinemia as an adverse effect.

In the 1990s, the atypical antipsychotics were developed, branded, and marketed with a dual serotonin-dopamine receptor antagonism (SDA) mechanism of action whereby they simultaneously block both D2 and serotonin-2A (5HT-2A) receptors allowing for adequate antipsychotic effectiveness while lowering the risk of extrapyramidal symptoms (EPS). This improved neuromuscular safety profile occurs as the 5HT-2A receptor antagonism allows these atypical antipsychotics to be more selective at dampening mesolimbic DA activity while allowing less interference in the nigrostriatal DA pathway (Schwartz et al, 2012)<sup>5</sup>.

**The glutamine hypothesis.** To be up to date, there is another hypothesis in the horizon that offers the glutamine hypothesis to explain the less than stellar results from the blocking of DA neurons. (Schawartz et al, 2012)<sup>5</sup>. Until more evidence is available, the dopamine hypothesis will continue to be the working hypothesis to explain the psychopharmacology of schizophrenia.

## TYPICAL ANTIPSYCHOTICS – FIRST GENERATION ANTIPSYCHOTICS (FGAS)

### Potency

The FGAs can be divided into 3 classes based on their potency of dopamine blockade in comparison to effects at other neurotransmitter receptors, and the dose needed to achieve therapeutic effectiveness. See Table 1.

### Mechanism of action

FGAs are antagonists at postsynaptic D2 receptors in the mesolimbic pathway. D2 blockade in the mesocortical pathways also occurs, which can worsen the cognitive and negative symptoms of schizophrenia. In addition to D2 antagonism, FGAs also have blockade effects at M1 muscarinic cholinergic receptors leading to anticholinergic symptoms of constipation, dry mouth, blurred vision, urinary symptoms, and sedation; blockade at H1 histamine receptors leading to sedation and weight gain; and blockade at alpha1-adrenergic receptors leading to dizziness, orthostatic hypotension, and sedation.

High potency D2 neuroreceptor blockers (e.g. Haloperidol) have more EPS and less histaminic e.g. sedation, alpha adrenergic (e.g. orthostatic hypotension) and anticholinergic effects (e.g. dry mouth) effects. Low potency D2 neuroreceptor blockers (e.g. Chlorpromazine) have fewer EPS but more H1,  $\alpha_1$ , and muscarinic blocking effects.

### Efficacy and indications

FGAs are indicated for treatment of the positive symptoms of schizophrenia and schizoaffective disorder in the acute stage as well as for long-term maintenance. Negative symptoms (e.g. apathy, anhedonia, avolition, and alogia, can be worsened through the use of these medications. Cognitive dysfunction and dysphoria are also observed when EPS emerges.

## ATYPICAL ANTIPSYCHOTICS – SECOND GENERATION ANTIPSYCHOTICS (SGAS)

Whilst the FGAs were successful at treating the symptoms of schizophrenia and triggering the deinstitutionalisation movement, most patients with psychotic disorders were still not able to regain social functioning. The search for medications to deal with FGA treatment-resistant patients resulted in the introduction of clozapine and other antipsychotics which are more effective than the FGAs for both the positive and negative symptoms of schizophrenia. These were the SGAs and were modelled after clozapine's neuroreceptor profile of greater serotonin 5-HT<sub>2A</sub> antagonism than dopamine D2 antagonism. Table 2 shows selected SGAs and the year they were introduced.

### Mechanism of action

SGAs employ both serotonin and dopamine antagonism to target symptoms, and this distinguishes them from the FGAs, the latter having mainly strong dopamine antagonism. In the SGAs, D2 antagonism tends to be more specific in they target mesolimbic and mesocortical pathways and have less effect on nigrostriatal pathways, leading to less risk of EPS. Of the SGAs, risperidone is different in that it has a higher affinity of the D2 receptor and hence has a dose related increase in EPS as well as prolactin.

Serotonergic antagonism occurs primarily at the 5-HT<sub>2A</sub> neuroreceptor. Blockade of these neuroreceptor in the cortex leads to decreased glutamate release from the cortical glutamate projections in the ventral tegmental area (VTA). This leads to decreased excitation of dopamine neurons in the VTA and further blockade of positive symptoms of schizophrenia.

SGAs also have some effects on cognitive, negative, and affective symptoms of schizophrenia. These symptoms are thought to be due to low dopamine activity in mesocortical pathways. 5-HT<sub>2A</sub> blockade leads to increased frontal dopamine (by releasing 5-HT inhibition of dopamine), which may be the

**TABLE 1. SELECTED FIRST GENERATION ANTIPSYCHOTICS**

Drug	Initial dose (mg)	Maintenance dose (mg)	Maximum dose (mg)	Dopamine D2 neuroreceptor potency
Chlorpromazine	75	200-400	1000	Low
Thioridazine	25-150	75-400	800	Low
Perphenazine	12-24	8-24	64	Medium
Fluphenazine	2.5-10	1-5	40	High
Haloperidol	2-6	12-18	40	High
Thiothixene	5-10	15-30	60	High
Trifluoperazine	2-15	6-20	80	High
Depot antipsychotics (long acting)				
Flupenthixol decanoate (Fluanxol depot)	5-40	20-80/4 weeks	80/2 weeks	High
Fluphenazine decanoate (Modectate)	2.5-12.5	12.5-100/2-4 weeks	50-100/2-4 weeks	High
Zuclopenthixol acetate (Clopixol acuphase)	50-150/2-3 days		150/day X 4 days	High
Zuclopenthixol decanoate (Clopixol)	100-400	150-300/2-4 weeks	400/2 weeks	High

**TABLE 2. SELECTED SECOND GENERATION ANTIPSYCHOTICS**

Drug	Year introduced	Usual daily dosage mg
Aripiprazole	2002	10-30
Clozapine	1989	300-600
Olanzapine	1996	10-20
Quetiapine	1998	250-600
Respiridone	1994	3-6
Ziprasidone	2001	40-80
Depot injection – Long acting antipsychotic		
Respiridone (Consta) Inj		25-37.5mg/2 weeks

mechanism with which these medications target these negative, cognitive and affective symptoms. In addition to 5-HT<sub>2A</sub> blockade, the SGAs have effects at other serotonin receptors. They also work at other DA receptors as well as muscarinic, histaminic, and alpha-adrenergic receptors. The SGAs may also have effect in the insulin regulation system.

Aripiprazole as a SGA deserves special mention as a partial D<sub>2</sub> agonist, leading to effective reduction in positive psychotic symptoms with minimal risk of EPS. In the mesolimbic pathways, aripiprazole exerts D<sub>2</sub> antagonism, leading to reduction of dopamine output and reduction of positive psychotic symptoms. In the nigrostriatal pathways, however, partial D<sub>2</sub> antagonism prevents reduction of dopamine tone and leads to normal functioning. Akathisia may however emerge transiently during the initiation of aripiprazole.

SGAs have low affinity to dopamine D<sub>2</sub> receptors and, compared to FGAs, dissociate more easily from D<sub>2</sub> neuroreceptors. Landmark positron emission tomography (PET) studies by Kapur and Seeman, 2001 (Hudepohl & Nasrallah, 2012), showed that transient occupancy (60-65%) of D<sub>2</sub> neuroreceptors is sufficient for antipsychotic activity and results in a lower incidence of EPS and other motor side-effects. This “hit and run” theory is common to the SGAs and explains improved tolerability of these medications. The PET D<sub>2</sub> occupancy studies also found that EPS emerges when 78% or higher occupancy of the D<sub>2</sub> neuroreceptors occur. (Hudepohl & Nasrallah, 2012)<sup>3</sup>.

### Efficacy and indications

All of the SGAs have an FDA indication for treatment of schizophrenia, for both acute exacerbation and long-term maintenance treatment. The SGAs are mainly effective for the treatment of positive symptoms (delusions, hallucinations, thought disorder), and to a lesser extent for negative symptoms (apathy, blunted affect, asociality, lack of motivation), and cognitive symptoms (impairments in executive functions and memory). Maintenance treatment is indicated to prevent psychotic relapse.

Clozapine has two unique indications in the treatment of schizophrenia. It is approved for use only in treatment-resistant

and refractory schizophrenia given its risk of agranulocytosis as a life threatening adverse effect. Current treatment recommendations state that a patient must fail an adequate trial of two SGAs prior to a trial of clozapine. It is also the only drug that is FDA-approved for the treatment and prevention of suicidality in patients with schizophrenia.

### ARE SGAs MORE EFFECTIVE THAN FGAs?

For two decades, the SGAs have dominated the market under the assumption that they are more effective than the FGAs. The results of two publicly funded trials in US designed to evaluate the effectiveness of the antipsychotics under real-world conditions have called into question these prescribing preferences.

**The Clinical Anti-psychotic Trials of Intervention Effectiveness study (CATIE).** This study was designed to compare the FGA perphenazine with several SGAs using “all cause discontinuation” as a proxy measure for effectiveness (Muench & Hamer, 2010; Lieberman et al, 2005)<sup>6,7</sup>.

**The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS).** This study measured quality of life and other effectiveness measures. (Muench & Hamer, 2010; Jones et al, 2006)<sup>6,8</sup>.

Neither study demonstrated a clear difference in effectiveness between FGAs and non-clozapine SGAs.

**Meta-analysis.** A meta-analysis in 2009 by Leucht et al of 150 double blind clinical trials, involving 21533 patients further clarified the situation. (Gupta, 2010; Leucht et al, 2009)<sup>10,11</sup>. Four SGAs were found to be better than FGAs for overall efficacy (both positive and negative symptoms). Among them, the effect size was largest for clozapine –0.52 (95% CI –0.75 to –0.29, P<0.001), olanzapine –0.28 (–0.38 to –0.18, p<0.0001) and lastly risperidone –0.18 (–0.22 to –0.05, p = 0.002). The other SGAs (aripiprazole, quetiapine, zotepine, ziprasidone, sertindole) were not more efficacious than FGAs, even on negative symptoms. EPS, expected, were prevalent in FGAs. On the other hand, SGAs (except ziprasidone and aripiprazole) induced more weight gain. Similarly, some drugs were better for depressive symptoms (namely, amisulpride, clozapine, olanzapine, aripiprazole, and quetiapine).

In the 2009 guideline, NICE no longer recommends SGAs as a first-line treatment which was its recommendation in 2002. (NICE, 2009)<sup>9</sup>

The implications of three studies quoted above and the position of NICE are now clear. SGAs are not always superior. In some patients, FGAs may be more effective and better tolerated than the SGAs. With the exception that clozapine is more effective for treatment resistant patients, the choice of antipsychotic should depend on the potential for adverse effects in individual patients. General comparison between the FGA and SGA classes are less helpful than comparisons among specific medications because each presents its own challenges in terms of balancing effectiveness with safety and tolerability. (Muench & Hamer, 2010)<sup>6</sup>.



Caring for your loved one starts here  
**careinmind.aic.sg**

## A one-stop online resource on mental wellness

If you are a caregiver or if you want to learn more about mental wellness, Care In Mind is an important information resource for you or your loved one.

From understanding common mental health conditions to finding a service provider who meets your needs, the Care In Mind website gives you essential information and resources. Post any question on mental health wellness on the website and have them answered. Service providers and partners can also discuss and exchange information using this website.

### What you can find on Care In Mind

- Answers to your questions
- Information on mental health conditions
- Service providers
- Self-care tips
- Information on mental wellness
- Resources to empower you



## ADVERSE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS

The use of antipsychotic medications is a balance between the benefit of relieving psychotic symptoms and the harm of troubling adverse effects.

As a class, the FGAs are more likely to be associated with EPS but this is primarily true of medications that bind tightly with D2 neuroreceptors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine. Anticholinergic effects are especially prominent with weaker-binding FGAs, as well as with the SGA clozapine.

As a class, the SGAs, especially clozapine and olanzapine generally tend to cause more problems relating to the metabolic syndrome, such as obesity and type 2 diabetes mellitus.

All antipsychotic medications are associated with an increased likelihood of sedation, sexual dysfunction, postural hypotension, prolonged QT interval and sudden death.

Primary care physicians need to be familiar with the individual adverse effect profiles of these medications. Vigilance for the occurrence of adverse effects, willingness to adjust or change medications as needed or work with psychiatric colleagues to do so, and the preparedness to treat any resulting medical sequelae will result in better functional outcome of patients with schizophrenia.

The comparative risk of these adverse effects amongst them are shown in Table 3.

## Extrapyramidal symptoms (EPS)

Antipsychotic medications cause four main extrapyramidal symptoms: pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia. The first three usually begin within a few weeks of starting a new medication (or increasing the dosage). These symptoms may cause discomfort, social stigma, and poor compliance.

**Pseudoparkinsonism.** This is a reversible syndrome of tremulousness in the hands and arms, rigidity in the arms and shoulders, bradykinesia, akinesia, hypersalivation, masked facies, and shuffling gait. The bradykinesia or akinesia can create a diagnostic dilemma, with symptoms resembling depression or even the negative symptoms of schizophrenia (i.e., an inability to pay attention, the loss of a sense of pleasure, the loss of will or drive, disorganization or impoverishment of thoughts and speech, flattening of affect, and social withdrawal). Dosage reduction helps.

**Akathisia.** This is a feeling of inner restlessness which can be manifested as excessive pacing or inability to remain still for any length of time. Differentiating akathisia from psychiatric anxiety and agitation can be difficult. Treatment consists of dosage reduction when possible, or the addition of a low-dose beta blocker, such as propranolol (Inderal) at 20 to 80 mg per day.

**TABLE 3. COMPARATIVE RISK OF ADVERSE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS\***

Adverse effect	Low potency FGAs@	High potency FGAs#	SGAs Aripiprazole	Clozapine	Olanzapine	Quetiapine	Respiridone	Ziprasidone
Extrapyramidal symptoms	+	+++	+	0	+	0	++	+
Sedation	+++	+	+	+++	++	++	+	+
Seizures	+	+	+	+++	+	+	+	+
Prolonged QT interval	++\$	+	+	+	+	+	+	++
Postural hypotension	+++	+	+	+++	+	++	++	+
Anticholinergic effects	+++	+	0	+++	+	+	0	0
Sexual dysfunction	+++	++	+	+	+	+	++	+
Hyper								
Prolactinemia	++	+++	0	0	+	0	+++	+
Neuroleptic malignant syndrome	+	++	+	+	+	+	+	+
Dyslipidemia	++	+	0	+++	+++	++	+	0
Type 2 diabetes mellitus	+	+	+	++	++	+	+	+
Weight gain	++	+	0	+++	+++	++	++	0

### NOTES

0 = rare; + = low risk; ++ = medium risk; +++ = higher risk

FGAs = first generation antipsychotics; SGAs = second generation antipsychotics

\* = Effects are approximate, and relative to other antipsychotic medications rather than absolute risk of an adverse effect occurring

@ = FGAs with lower potency dopamine D2 neuroreceptor blockade, including chlorpromazine and thioridazine

# = FGAs with higher potency dopamine D2 neuroreceptor blockade, including fluphenazine, haloperidol, thiothixene, and trifluoperazine. Please note that the FGA perphenazine is considered to have intermediate dopamine D2 neuroreceptor blockade, with an adverse effect profile between the low- and high-potency FGAs

\$ = individually, thioridazine has a higher risk of prolonged QT interval and should be used only when no other appropriate options are available.

SOURCES: Muench & Hamer, 2010; Haddad & Shama, 2007; Gardner et al, 2005.

**Dystonic reactions.** These are spastic contractions of the muscles, including oculogyric crisis, retrocollis, torticollis, trismus, opisthotonos, or laryngospasm. These uncomfortable reactions can be life threatening if left untreated. Intervention requires administration of intravenous or intramuscular anticholinergic agents.

**Tardive dyskinesia.** This is an involuntary movement disorder occurring with long-term antipsychotic treatment; it may not be reversible even if the medication is discontinued. Tardive dyskinesia usually involves the orofacial region, but all parts of the body can be involved. Abnormal movements can include myoclonic jerks, tics, chorea, and dystonia. They become most evident when patients are aroused, but ease during relaxation and disappear during sleep. Risk factors for developing tardive dyskinesia include long-term therapy with FGAs at higher dosages, older age, female sex, and concurrent affective disorders. Attempts to treat tardive dyskinesia usually consist of discontinuing the offending agent.

### **Sedation**

Sedation is common with antipsychotic medications and is dose related. It can be a cause of poor compliance and, if persistent, can interfere with social and vocational functioning. Low-potency FGAs and clozapine are the most sedating, with some effect from olanzapine and quetiapine. Somnolence can be alleviated by lowering the dosage, changing to a single bedtime dose, or switching to a less sedating medication.

### **Seizures**

All antipsychotics can lower the seizure threshold. They should be used with caution in patients who have a history of seizures and in those with organic brain disorders. Depot antipsychotics should not be used in patients with epilepsy because they cannot be quickly withdrawn.

### **Prolonged QT interval**

All antipsychotics can contribute to prolongation of ventricular repolarization (prolonged QT interval), which can in turn lead to torsades de pointes and sudden cardiac death. This effect is most marked with the low-potency FGA thioridazine and the SGA ziprasidone, and is dose dependent. The incidence of sudden cardiac death among patients taking antipsychotics is about twice that of the general population.

### **Postural hypotension**

Orthostatic hypotension can occur with all antipsychotic medications, depending on the degree of  $\alpha_1$ -adrenoreceptor antagonism, particularly with low-potency FGAs and clozapine. It can also occur with risperidone and quetiapine, especially with rapid titration. This effect is more common in older adults (with risk of falls), those on blood pressure medications, and those who have other cardiovascular diseases. With careful dose

titration, patients may become tolerant to this effect. Decreasing or dividing doses or switching to a medication with a lesser antiadrenergic effect are treatment options.

### **Anticholinergic effects**

Constipation, urinary retention, dry mouth, blurred vision and, at times, cognitive impairment are highly likely adverse effects of the low potency FGAs. Olanzapine and quetiapine also have been shown to do so at high dosages. Medication doses can be lowered or divided to reduce this problem.

### **Sexual dysfunction**

Some 40% patients taking antipsychotic medications report problems with sexual dysfunction, which can lead to poor medication adherence. Use of antipsychotics can affect all phases of sexual function, including libido, arousal, and orgasm. Both FGAs and SGAs can impair arousal and orgasm in men and women.

### **Hyperprolactinemia**

Antipsychotics cause high prolactin levels by blocking the normal tonic inhibition on pituitary mammatropic cells of dopamine produced in the hypothalamus. Hyperprolactinemia is common with the use of any FGA, as well as with the SGA risperidone and is dose dependent. Hyperprolactinemia can be asymptomatic, but may cause gynecomastia, galactorrhea, oligo- or amenorrhea, sexual dysfunction, acne, hirsutism, infertility, and loss of bone mineral density. Symptoms often appear within a few weeks of beginning the antipsychotic or increasing the dosage, but can also arise after long-term stable use. Presence of osteoporosis, sexual side effects, or prolactin-dependent breast cancer may necessitate switching to an antipsychotic that does not raise prolactin levels, such as aripiprazole or quetiapine.

### **Neuroleptic malignant syndrome**

Neuroleptic malignant syndrome (NMS) is an idiosyncratic, life-threatening complication of treatment with antipsychotic drugs. The criteria for diagnosis are fever, severe muscle rigidity, and two of the associated symptoms: autonomic (namely diaphoresis, tachycardia), and mental changes (confusion to coma, mutism). The patient should be treated promptly: the causative drugs is stopped, the patient rehydrated, muscle relaxants like dantrolene or baclofen be considered and ventilator support if needed. Benzodiazepines can be given in severe agitation. Further investigations include blood counts, cultures, urine toxicology. The condition carries a risk of death and multi-organ failure, but given adequate supportive treatment the prognosis is good and there are usually no lasting sequelae. Approximately 2 weeks after resolution of NMS, treatment with a low-potency atypical antipsychotic should be started at a low dose and slowly titrated in a monitored setting with careful assessment for signs of recurrent NMS. (Kipps et al, 2005)<sup>14</sup>

## ANTIPSYCHOTIC INDUCED WEIGHT GAIN

Weight gain is a common adverse effect of using anti-psychotic medications, and can be rapid and difficult to control. Weight gain does not seem to be dose dependent within the normal therapeutic range. The effect is worse with clozapine and olanzapine; minimal with aripiprazole and ziprasidone; and intermediate with other antipsychotics, including low-potency FGAs.

Antipsychotic medications can contribute to a wide range of glycemic abnormalities, from mild insulin resistance to diabetic ketoacidosis, as well as worsening of glycemic control in patients with preexisting diabetes. Although FGAs and SGAs can cause these problems, risk is variable—the greatest risk is with clozapine and olanzapine.

Dyslipidemia is also associated with several antipsychotic medications, with increases noted primarily in triglyceride levels. Low-potency FGAs and the SGAs clozapine, olanzapine, and quetiapine are associated with a higher risk of hyperlipidemia. Overall, metabolic disturbances appear to be greatest with clozapine and olanzapine, intermediate with quetiapine and low-potency FGAs, and lowest with aripiprazole, risperidone, ziprasidone, and high-potency FGAs.

## RECOMMENDATIONS ON THE USE OF MEDICATIONS IN THE DIFFERENT PHASES OF THE DISEASE

### Acute phase management

- Prevent harm by hospitalisation.
- Reduce aggression and threat by rapid tranquilisation (oral lorazepam 1 to 2mg stat, olanzapine zydis 10mg stat or risperidone quicklet 1-2mg stat; if patient refuses oral medication, consider IM lorazepam 2mg stat, and/or IM haloperidol 5-10mg stat).
- Reduce acute symptoms by regular oral antipsychotics. Start at low dose and titrate upwards over 2 weeks. The choice of antipsychotics is based on risk and benefit ratio and patient's preference after explanation of various options. Close monitoring for 2 months to assess effectiveness.

### Initial treatment (MOH CPG 2011)<sup>15</sup>

- The patient's social supports, functioning and relative risk of self-harm or harm to others must be evaluated for choice of treatment setting.
- People newly diagnosed with schizophrenia should be offered oral antipsychotic medication. The recommended optimal oral dose of antipsychotics is 300–1,000 mg chlorpromazine equivalents daily for an adequate duration of 4–6 weeks.
- If there is inadequate response by 4–6 weeks or if patient

develops intolerable side effects, the medication should be reviewed and another typical or atypical antipsychotics should be used.

- Long-acting depot antipsychotics should not be used for acute episodes because it may take 3–6 months for the medications to reach a stable steady state.
- Electroconvulsive therapy should be considered for patients who have not responded to an adequate trial of antipsychotics and for patients with life threatening symptoms such as catatonia and prominent depressive symptoms.

### Stabilisation phase

- Offer psychoeducation to enhance knowledge of illness.
- Minimize the likelihood of relapse by ensuring compliance to medications. Long-acting depot (e.g. IM fluanxol, clopixol). antipsychotics may be indicated in patients in whom treatment adherence is an issue or when a patient expresses a preference for such treatment (MOH CPG 2011)<sup>15</sup>
- Reduce expressed emotion by family intervention.
- Enhance adaptation and coping to social and occupational disturbances by rehabilitation and occupational therapy.
- Facilitate continued reduction in symptoms and promote the process of recovery by psychological interventions e.g. cognitive behaviour therapy and problem solving therapy.
- Antidepressants should be considered when depressive symptoms emerge during the stable phase of schizophrenia (post-psychotic depression). Antidepressants should be used at the same dose as for treatment of major depressive disorder (MOH CPG 2011)<sup>15</sup>.

### Maintenance phase

- Ensure symptom remission or control by the lowest effective dose of antipsychotics, which should not be lower than half of the effective dose during the acute phase (MOH CPG 2011)<sup>15</sup>.
- Monitor and manage adverse effects related to antipsychotics.
- Regular follow-up with a psychiatrist on a regular basis.
- For patient with poor social support, refer to the community psychiatric team for home visit.
- Oral antipsychotics should be used as first-line treatment for patients with an acute relapse of schizophrenia (MOH CPG 2011)<sup>15</sup>.
- Patients receiving atypical antipsychotics should be monitored regularly for metabolic side effects (MOH CPG 2011)<sup>15</sup>.
- Treatment options for schizophrenia patients who are pregnant should be individualised, with consideration of severity of previous episodes, previous response to treatment and the woman's preference. Abrupt cessation of medications should be avoided. (MOH CPG 2011)<sup>15</sup>.



## REFERENCES

1. Mackin P, Thomas SH. Atypical antipsychotic drugs. *BMJ*. 2011 Mar 4;342:d1126. doi: 10.1136/bmj.d1126. PubMed PMID: 21378070.
2. Agid O, Mamo D, Ginovart N, Vitcu I, Wilson AA, Zipursky RB, et al. Striatal vs extrastriatal dopamine D2 receptors in antipsychotic response—a double-blind PET study in schizophrenia. *Neuropsychopharmacology* 2007;32:1209-15.
3. Hudepohl NS, Nasrallah HA. Antipsychotic drugs. *Handb Clin Neurol*. 2012;106:657-67. doi: 10.1016/B978-0-444-52002-9.00039-5. Review. PubMed PMID: 22608650.
4. Nasrallah HA, Tandon. Classic antipsychotic medications. In: AF Schatzberg, CB Nemeroff (eds). *The American Psychiatric Publishing Textbook of Psychopharmacology*. 4th ed. American Psychiatric Publishing, Arlington, 2009:553-4.
5. Schwartz TL, Sachdeva S, Stahl SM. Glutamate neurocircuitry: theoretical underpinnings in schizophrenia. *Front Pharmacol*. 2012;3:195. doi: 10.3389/fphar.2012.00195. Epub 2012 Nov 26. PubMed PMID: 23189055; PubMed Central PMCID: PMC3505861.
6. Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician*. 2010 Mar 1;81(5):617-22. Review. PubMed PMID: 20187598.
7. Lieberman JA, Stroup TS, Mcevoy JP, et al., for the Clinical Antipsychotic Trials of Intervention effectiveness (CATIE) Investigators. effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-23.
8. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*. 2006;63(10):1079-87.
9. National Institute for Health and Clinical Excellence. Core interventions in the treatment and management of schizophrenia in primary and secondary care (update). (Clinical guideline 82.) 2009. [www.nice.org.uk/CG82](http://www.nice.org.uk/CG82).
10. Gupta S. First-generation vs second-generation antipsychotic drugs: The ongoing saga. *Indian J Psychiatry*. 2010 Jan;52(1):77. doi:10.4103/0019-5545.58904. PubMed PMID: 20174527; PubMed Central PMCID: PMC2824991.
11. Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet*. 2003;361(9369):1581-9.
12. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs*. 2007;21(11):911-36.
13. Gardner DM, Baldessarini RJ, Warchick P. Modern antipsychotic drugs: a critical overview. *CMAJ*. 2005;172(13):1703-11.
14. Kipps CM, Fung VS, Grattan-Smith P, de Moore GM, Morris JG. Movement disorder emergencies. *Mov Disord*. 2005 Mar;20(3):322-34. Review. PubMed PMID: 15584031.
15. Verma S, Chan LL, Chee KS, Chen H, Chin SA, Chong SA, Chua W, Fones C, Fung D, Khoo CL, Kwek SK, Ling J, Poh P, Sim K, Tan BL, Tan C, Tan CH, Tan LL, Tay WK; MOH Clinical Practice Guidelines Workgroup on Schizophrenia. Ministry of Health clinical practice guidelines: schizophrenia. *Singapore Med J*. 2011 Jul;52(7):521-5; quiz 526. PubMed PMID: 21808964.

## LEARNING POINTS

- **Antipsychotics are a pharmacologically heterogeneous group of compounds, but all act as D2 dopamine receptor antagonists, an action linked to their antipsychotic effect.**
- **As a class, the FGAs are more likely to be associated with EPS but this is primarily true of medications that bind tightly with D2 neuroreceptors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine.**
- **Anticholinergic effects are especially prominent with weaker-binding FGAs, as well as with the SGA clozapine.**
- **As a class, the SGAs, especially clozapine and olanzapine generally tend to cause more problems relating to the metabolic syndrome, such as obesity and type 2 diabetes mellitus.**
- **All antipsychotic medications are associated with an increased likelihood of sedation, sexual dysfunction, postural hypotension, prolonged QT interval and sudden death.**