Providing an overview on antipsychotics: schizophrenia a psychiatric challenge? A 2017 Update

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Abstract

Psychosis is an umbrella term used in the description of various conditions involving delusions and hallucinations. This article focuses mainly on the management of schizophrenia. Schizophrenia is a complex disorder, which provides many pharmacotherapy-related challenges. Advances have been made in the treatment of the condition; however, this requires a team approach, with the pharmacist having to monitor treatment both for safety and efficacy. The involvement of medicines that might modulate the N-methyl-D-aspartate (NMDA) receptors is an exciting development that should be monitored.

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Introduction

Psychosis has various definitions, with the most basic referring to a psychotic episode as an event that involves delusions and prominent hallucinations, without the affected patient being aware of the pathological nature of the hallucinations. Some definitions include the positive symptoms experienced in schizophrenia, such as disorganised speech and grossly disorganised or catatonic behaviour. The use of the term 'psychotic' also differs between schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder and a psychotic disorder due to a general medical condition or substance-induced psychotic disorder, where the term refers to delusions or hallucinations that are not accompanied by insight.[1]

Schizophrenia is characterised by three major symptom domains: positive, negative (e.g. social withdrawal, flattened affect) and cognitive symptoms (e.g. deficits in working memory).[1]

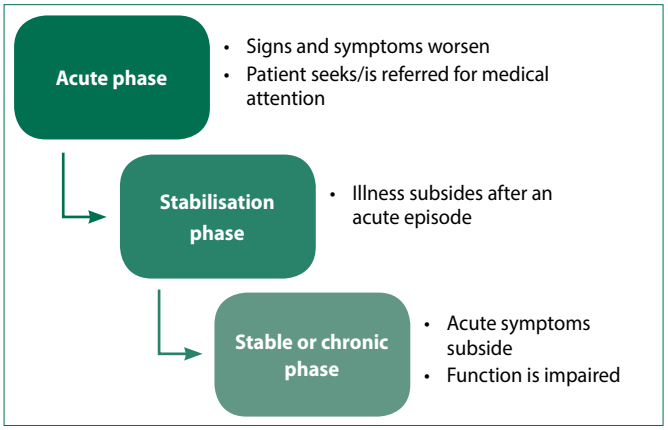


Figure 1: Schizophrenia evolution

As shown in Figure 1, three stages are identified in the evolution of schizophrenia and are of importance to the pharmacist when managing or evaluating treatment.[2]

Neurotransmitter involvement

Dopamine

The hypothesis of dopamine involvement in the development of schizophrenia follows two ideas:[3]

- Dopamine involved in antipsychotic action: Increased densities of D_2 receptors have been shown in the caudate nucleus and decreased densities in the prefrontal cortex. The over-activity of these receptors in the mesolimbic part of the brain provides an explanation of the positive symptoms. These receptors provide the mechanistic basis for the antipsychotic action observed when blocked.
- Decreased activity in mesocortical dopaminergic pathway: Neuroimaging studies have shown that patients diagnosed with schizophrenia and suffering from psychosis show a decreased activity of D_1 receptors in the mesocortical dopamine pathway.

To manage schizophrenia pharmacologically, inhibition of dopaminergic transmission has to be inhibited in the limbic pathway whilst enhancing the dopaminergic transmission in the prefrontal cortex. This makes managing schizophrenia challenging. Most current antipsychotics act on this system to manage mainly positive symptoms.

NMDA and glutamate

There is a growing body of evidence that supports glutamate dysfuntion as a contributing factor to the disease.[4] Glutaminergic and GABAergic neurons have an important role in controlling

neuronal activity in the mesolimbic pathway, where there is also dopaminergic activity.[4] It is for this reason that the glutamate synapse has now received widespread attention as an important target for pharmacological action.[4] The synapse is target rich, as it contains a large number of presynaptic, postsynaptic and regulatory proteins that may be used in drug therapy to treat symptoms refractory to other drug therapy.[5] It has been postulated that some of the negative symptoms seen in schizophrenia might be due to a disruption in glutamate transmission at the NMDA receptors owing to functional abnormalities of these receptors.[5] This has further been supported by the observation that administration of NMDA receptor antagonists such as ketamine induce a schizophrenia-like state.[4] Drug development for the management of schizophrenia might be steered towards the development of agents that enhance the function of NMDA receptors by activating the glycine site.[5] Glutamatergic agents are at various stages of development, including the glycine transport inhibitors bitopertin and sarcosine.[6]

Serotonin

Serotonin does not seem to have a direct role in the pathogenesis of schizophrenia; however, its receptors are present on the dopaminergic axons.[5,6] Stimulation of these receptors decreases dopamine release, especially in the striatum.[5,6] Drugs with combined D_2 antagonistic effects and 5-HT-receptor activity have improved therapeutic effects, as discussed later.[5,6]

Management of psychosis

Baseline investigations prior to initiation of therapy

All antipsychotics increase body weight, although to varying degrees, and some second-generation antipsychotics (SGAs) elevate lipid levels.[7] Some first-generation antipsychotics (FGAs) (e.g. clozapine) produce agranulocytosis.[7] It is for this reason that all patients undergo the following baseline investigations prior to initiation of antipsychotic agents:[7]

- body mass index (especially for olanzapine)
- waist-to-hip ratio
- fasting blood glucose
- liver function tests
- white cell count, specifically acute neutrophil count (especially for clozapine)
- electrocardiogram.

These baseline investigations can be modified depending on the regimen to be initiated or if there is a change in regimen. The pharmacist can assist in monitoring the side effect profile.

Pharmacological management

Although psychosocial interventions are crucial in promoting recovery and improving quality of life for the schizophrenia patient during clinical management of different stages of the illness, pharmacological management is the essential component of treatment.[7,8]

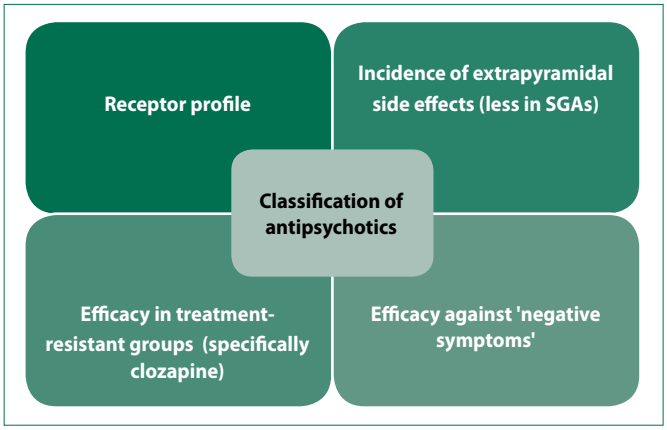


Figure 2: Distinction between FGAs and SGAs[5,7]
SGA: second-generation antipsychotics

Monotherapy is recommended. There is no advantage in combining antipsychotics, which should be done only for short periods when switching agents or in the treatment-resistant setting.[7]

Medication must be individualised, as the individual response is highly variable. The patient's immediate presenting problem must be considered first and their prior response to pharmacotherapy including efficacy and side effects. The elderly and patients with their first episode of psychosis require lower doses.[7,8]

Schizophrenia is managed by typical antipsychotics (FGAs) or atypical antipsychotics (SGAs). SGAs are increasingly replacing FGAs as first-line treatment.[2,7] FGAs and SGAs may be distinguished and subsequently classified according to the following factors:[5,7]

First-generation antipsychotics

FGAs are antagonists of the dopamine (D_2) receptors in the mesocortex and limbic system and are more selective to D_1, D_4 and serotonin receptors compared to D_2. FGAs inhibit dopamine receptors in the nigrostriatal pathway and have an inhibitory effect at the histaminic and muscarinic receptors, giving rise to the characteristic extrapyramidal side effects.[8] There is a strong correlation between the therapeutic doses of these drugs and their binding affinity for the D_2 receptor site.[8]

Classification of first-generation antipsychotics

Phenothiazine derivatives

These compounds have antihistaminic, anticholinergic, anti-dopaminergic and adrenolytic properties.[9,10] Chlorpromazine is the prototype for this group. The least potent of the group are the aliphatic derivatives (chlorpromazine) and piperadine derivatives (thioridazine). Piperazine derivatives are more potent (effective in lower doses), but not necessarily more efficacious.[9,10]

Butyrophenones

These compounds largely lack antihistaminic, anticholinergic and adrenolytic activity, and are also non-sedative in therapeutic doses. However, they have greater extrapyramidal effects than phenothiazines.[9,10] Haloperidol, which is a potent neuroleptic, is the most widely used typical antipsychotic medicine.[9,10]

Table I: Recommended daily maximum doses of typical antipsychotics, their side effects and the associated management[11]

Name	Brand name	Usual dose	Maximum dose	Indication(s)	Side effects
Chlorpromazine	Largactil®	75–300 mg	1000 mg	Schizophrenia, intractable hiccups, to reduce the manic phase of manic depressive disorders	Postural hypotension (especially in the elderly), anticholinergic effects
Haloperidol	Serenace®	1.5–15 mg	20 mg	Schizophrenia, secondary psychosis	Oligomenorrhea or amenorrhea, extrapyramidal
Haloperidol decanoate	Haloperidol LA®	50 mg	300 mg	Tourette's syndrome	Orthostatic hypotension, seizure (rare)
Flupenthixol decanoate	Fluanxol®	40 mg	400 mg	Mild to moderate depression with or without anxiety	Insomnia
Fluphenazine decanoate	Modecate®	12.5 mg	100 mg	Psychotic disorders, especially schizophrenia	Blood dyscrasia
Zuclopenthixol	Clopixol®	200 mg	600 mg	Schizophrenia, including agitation, psychomotor disturbances, hostility, suspiciousness, aggressive affective reactions	Insomnia
Sulpiride	Eglonyl®	200–800 mg	2400 mg	Acute schizophrenic episodes and prevention of relapse in chronic cases	Fatigue, weight gain, erectile dysfunction
Pimozide	Orap®	2–20 mg	20 mg	Maintenance treatment of chronic schizophrenics who respond to the anti-hallucinatory and anti-delusional effects of classical neuroleptics but who do not need, or are handicapped by, the hyposedative action of such neuroleptics	Anorexia, akinesia, extrapyramidal side effects, sedation, visual disturbance, constipation, dry mouth

Table II: Recommended daily maximum doses of SGAs, their side effects and the associated management[11]

Name	Brand name	Usual dose	Maximum dose	Indication(s)	Side effects
Amisulpride	Solian®	400–800 mg	1200 mg	Acute and chronic schizophrenia	Neuroleptic malignancy syndrome
Aripiprazole	Abilify®	10–30 mg	30 mg	Schizophrenia, bipolar mania	Weight gain, anxiety, insomnia, headache
Clozapine	Clozaril®	200–450 mg	900 mg	Schizophrenia	Agranulocytosis, weight gain, hypotension
Olanzapine	Zyprexa®	10–20 mg	20 mg	Management of the manifestations of psychotic disorders, preventing the recurrence of manic episodes of bipolar disorder	Bradycardia, xerostomia, weight gain (dose dependent), hypercholesterolaemia, EPS (dose dependent), hyperglycaemia, weakness
Risperidone	Risperdal®	4–6 mg	16 mg	Acute and chronic schizophrenia, conduct and disruptive behaviour disorders in children 5–12 years of age	Angioedema, body temperature dysregulation, hyperprolactinaemia in children, insomnia
Quetiapine	Seroquel®	300–450 mg	750 mg	Bipolar mood disorder associated with mania, schizophrenia	Abdominal, back, chest or ear pain, dry mouth, somnolence
Ziprazidone	Geodon®	80 mg	160 mg	Acute exacerbation and maintenance of clinical improvement during continuation therapy in schizophrenia	Headache, nausea, extrapyramidal symptoms, generalised tonic-clonic seizures
Paliperidone	Invega®	50 mg	800 mg	Schizophrenia, schizoaffective disorder in adults (unlicensed indication)	Somnolence, dizziness, liver enzyme abnormalities, orthostatic hypotension and syncope, weight gain and metabolic dysfunction (particularly in adolescents)

Benzamides

Amisulpride, a substituted benzamide analogue of sulpiride, is a highly selective antagonist of D_2 and D_3 receptors, with little affinity for D_1-like or non-dopaminergic receptors.[8]

FGAs differ in potency, not effectiveness.[10] For example, haloperidol and fluphenazine have a high potency, perphenazine and loxapine have a mild potency and chlorpromazine has a low potency.

Table I provides an overview of the first-generation medicines used in the management of schizophrenia.

Second-generation antipsychotics

There are two theories on the mechanism of action of SGAs:

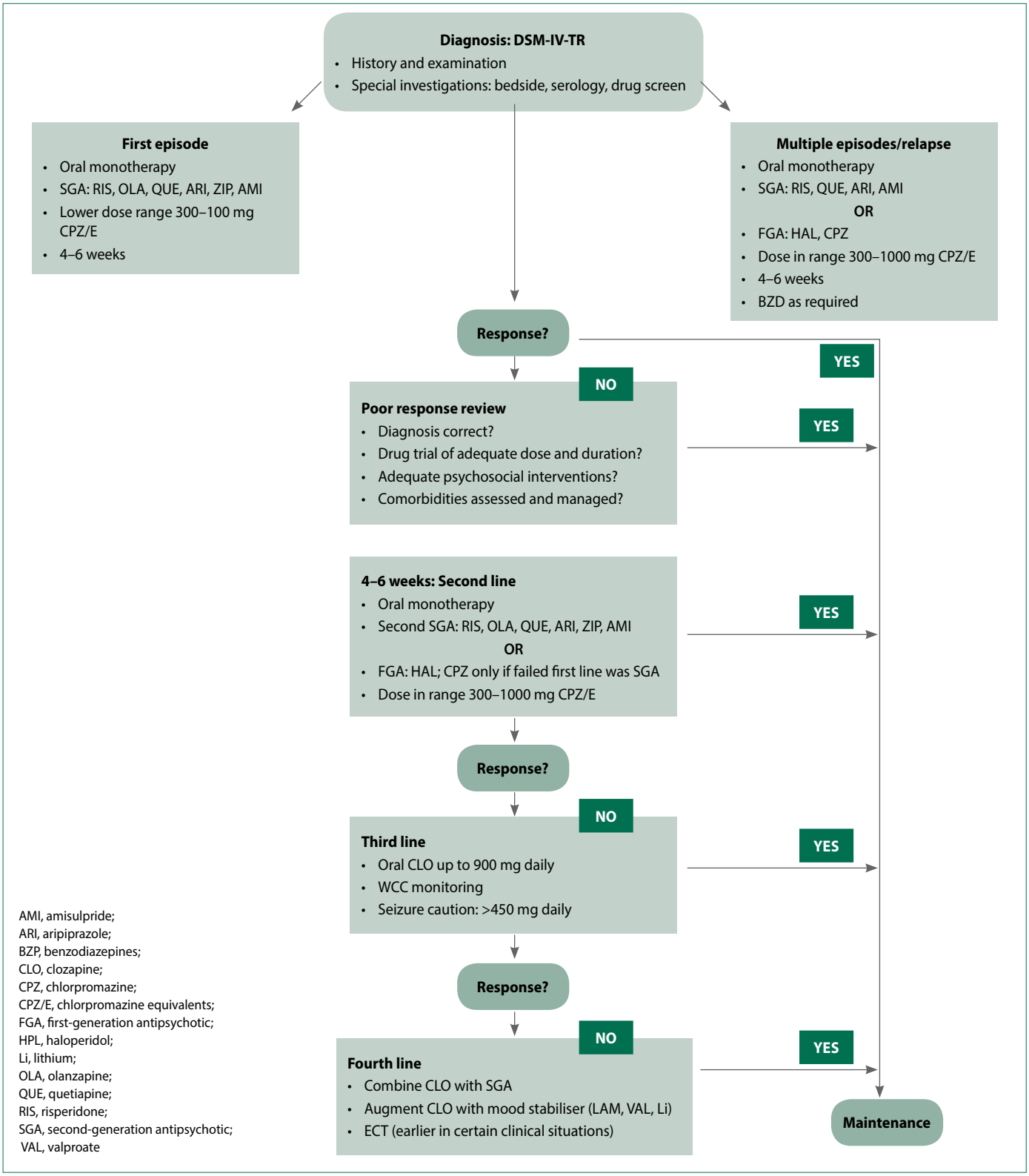
- The serotonin–dopamine (S_2/D_2) antagonist theory suggests that an SGA has a higher affinity for the serotonin 5-HT_{2A} receptor than for the dopamine D_2 receptor.
- The fast-off D_2 theory suggests that although an SGA cannot function without some degree of binding to D_2 receptors, it is the rate at which the drug dissociates from the receptor that is responsible for the effect. The theory suggests that dissociation from the D_2 receptor quickly makes the antipsychotic more accommodating of physiological dopamine transmission.[8,9,10]

Table III: Management strategies for side effects of antipsychotic medicine[12,13]

Effect	Strategies
Neuromotor effects	
Acute dystonia (e.g. involuntary, sustained muscle spasms, oculogyric crisis)	Select antipsychotic with low incidence of extrapyramidal effects
Chronic dystonia (e.g. sustained, involuntary spasms of skeletal muscles)	• Start with low dose and increase gradually • Add anticholinergic agent (e.g. benztropine)
Akathisia (feeling of 'inner restlessness', with a drive to move)	Reduce dose or switch medicine
Parkinsonism (e.g. masked facies, muscle rigidity, tremor, shuffling gait)	• Reduce dose or select antipsychotic with low risk for akathisia and increase dose slowly • Add a beta blocker (e.g. propranolol), benzodiazepine or mirtazapine • Reduce dose of antipsychotic medicine • Switch from FGA to SGA • Administer oral anticholinergic medicine
Tardive dyskinesia (e.g. orobuccofaciolingual movements)	• Select antipsychotic medicine with low risk for tardive dyskinesia • Evaluate risk factors for tardive dyskinesia • Switch to clozapine or other SGA
Anticholinergic effects	
Dry mouth	• Reduce dose or select antipsychotic agent with lower risk • Drink small amounts of fluid frequently • Use other oral hygiene products for dry mouth
Excessive saliva	Administer sublingual atropine, oral hyoscine hydrobromide or oral benztropine
Constipation	• Advise high-fibre dietary supplementation • Increase physical activity and fluid intake • Administer laxatives
Urinary incontinence	• Reduce dose, if feasible • Switch to another antipsychotic agent • Management depends on the underlying aetiology • Avoid high intake of fluids in the evening and ensure adequate voiding at bedtime
Cardiovascular effects	
Orthostatic hypotension	• Titrate dose gradually • Advise patient to stand up slowly from a sitting or lying position • Decrease or divide dose of antipsychotic medicine • Switch to another antipsychotic without anti-adrenergic effects
Tachycardia	• Switch medicine or add a low-dose peripheral beta blocker
QTc prolongation	• Avoid combining medicines with a known QTc prolongation • If QTc >450/470–500 ms or has increased more than 30–60 s, switch to another antipsychotic
Hyperprolacticnaemia	
Sexual dysfunction	• Evaluation of prolactin levels • Exclusion of pituitary tumour • Switch to a prolactin-sparing agent if there are symptoms of sexual or menstrual dysfunction. In women, discuss the risk of pregnancy and appropriate contraception
Risk of osteoporosis	Bone density screening; switch medicine if abnormal
Sedation	• Titrate the dose slowly • Reduce dose if applicable • Avoid concomitant use of other CNS depressants
Metabolic effects	
Obesity	• Switch to an antipsychotic with low risk of weight gain • Avoid polypharmacy if possible • Provide appropriate advice about lifestyle interventions (diet and exercise)
Diabetes	• Consider metformin • Monitor serum glucose, treat with diet and hypoglycaemic medicines as indicated • Monitor for complications of diabetes
Hypertension	Monitor blood pressure, treat with antihypertensive medication if indicated
Elevated cholesterol and lipids	• Switch to antipsychotic medicine with low risk of elevating cholesterol and lipids • Monitor lipid profile every 6–12 months • Treat with statin if lifestyle interventions (diet and exercise) are insufficient

CNS, central nervous system; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic

Figure 3: Treatment algorithm for schizophrenia



SGAs are generally associated with a lower risk of extrapyramidal side effects and tardive dyskinesia compared with FGAs, but they may be associated with higher rates of weight gain and metabolic disorders. Table II provides an overview of the SGAs used in the management of schizophrenia,[11] followed by Table III, which provides management strategies for side effects of antipsychotic medicine.[12,13]

General management principles in schizophrenia

Owing to their lack of extrapyramidal side effects and tardive dyskinesia, SGAs, excluding clozapine, have become agents of choice when treating first-time episodes or younger patients.[7,11] Monotherapy is recommended as there is no advantage to

combining antipsychotics.[7] Rispiridone, amisulpride, olanzapine, quetiapine, aripiprazole and ziprazidone are effective agents in the treatment of a first episode in psychotic patients.

When the response to the first-line agent is not satisfactory, another SGA can be considered or the choice of FGA can be changed. The second agent should be tried for a period of 4–6 weeks before considering a third line of treatment.[7]

Clozapine is commonly recommended for treatment of patients who experience inadequate control following trials with two different classes of antipsychotic or who display consistent aggression or persistent suicidal thoughts or behaviour.[2,5,10] The main safety concerns for clozapine are, however, agranulocytosis, myocarditis and diabetes.[2]

Clozapine is used as a third-line therapy, at the highest tolerable dose (<900 mg daily) for six months. Switching requires tapering and stopping the previous agent before initiating clozapine to reduce the risk of haematological side effects.[7,11]

Various adjunctive treatments, including benzodiazepines, lithium, anticonvulsants, antidepressants, beta blockers and dopamine agonists, have been used to enhance the response to antipsychotic medications or to treat residual symptoms of chronic schizophrenia and comorbid conditions with schizophrenia.[8]

Studies to determine the efficacy and effectiveness of FGAs compared with SGAs deliver conflicting results. A lower incidence of extrapyramidal side effects are seen with SGAs, although weight gain is a notable problem with these agents.[6] Drugs from both groups are equally effective in treating psychosis, with the SGAs providing greater treatment results when managing negative symptoms.[7] The choice of drug is consequently determined by:[7]

- availability and accessibility of the drug
- shared patient-centred decision making
- previous experience (efficacy and side effects)
- tailoring the side effect profile to meet the needs of the patient
- choice of mode of administration (oral or parenteral)

The pharmacist can greatly assist in finding the right choice of drug for the patient. Figure 3 shows a treatment algorithm for the management of schizophrenia.[7]

Conclusion

Schizophrenia is a complex disorder in which many aetiologies have a role. Management of the patient requires a multidisciplinary team, with each member of the team contributing to the patient's best care. Side effect profiles differ between the two groups of antipsychotics and the choice of drug should not only focus on the patient's characteristics but also involve the patient actively. Pharmacotherapy should be monitored according to the safety and efficacy of the drug with each patient visit.

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