Pharmacological Treatment of Schizophrenia

a report by
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Schizophrenia affects approximately 1% of the population worldwide and, in around 80% of those, it is a lifelong, disabling disorder. Both genetic and environmental factors contribute to the development of the disorder.

The symptoms of schizophrenia can be classified into three groups:

- positive symptoms (e.g. hallucinations and delusions);
- negative symptoms (e.g. anhedonia, social withdrawal and lack of initiative and energy); and
- disorganisation (e.g. incoherence, loose associations and poverty of thought content).

Cognitive impairment and deterioration are core features of schizophrenia and they are strongly related to disability.

Short History of Antipsychotic Drugs

Drug therapy has been the main treatment modality for schizophrenia. Chlorpromazine, the first modern antipsychotic drug, was introduced into psychiatry in 1952. It was followed by a number of other antipsychotics (e.g. haloperidol and thioridazine), also called neuroleptics because of their neurological side effects, such as Parkinsonian syndrome and tardive dyskinesia. The antipsychotic properties of these drugs were inseparable from extrapyramidal effects.

Clozapine was introduced into psychiatry in Europe in the 1970s and in the US in the 1990s. The frequency of the extrapyramidal neurological side effects of clozapine is comparable with placebo. Clozapine was followed by the introduction of other antipsychotics (e.g. risperidone and olanzapine) with low frequency of neurological adverse events. As the term 'neuroleptic' was no longer appropriate for these new drugs, the term 'atypical neuroleptics' and later 'second-generation antipsychotics' was introduced. Dopamine, especially dopamine-2, and later serotonin and other neurotransmitter receptors were identified as targets for antipsychotic drugs.

First-generation Antipsychotics

Many of the first-generation antipsychotics – e.g. flupentixol, haloperidol, perphenazine, trifluoperazine and thiothixene – are much more potent at blocking dopamine receptors than chlorpromazine. Increased potency of these drugs was not related to increased effectiveness, but to higher incidence and prevalence of extrapyramidal side effects caused mainly by dopamine blockade of the basal ganglia.

The first-generation antipsychotics had a dramatic effect on the life of patients suffering from schizophrenia. About 20% of the patients had full remission and, based on the results of two-year studies, only approximately 30% to 40% of the patients relapsed during treatment with first-generation antipsychotics, compared with approximately 80% without treatment.

First-generation antipsychotics effectively treat positive symptoms, but their efficacy is limited in the treatment of negative symptoms and they can even cause negative symptoms, such as anhedonia. They have little effect on the depression and suicidal behaviour of patients suffering from schizophrenia. Approximately 10% of these patients commit suicide. The side effects of these drugs include neurological syndromes (such as Parkinsonian syndrome, akathisia, tremor and tardive dyskinesia), hyperprolactinaemia, anhedonia, sedation, disturbances of thermoregulation, cardiac arrhythmias and weight gain. The neurological side effects contribute to the stigmatisation of the patients; young people often start shuffling, shaking and have visible salivation.

First-generation antipsychotics are available in different formulations, such as acute intramuscular injections, liquid form, tablets and in depot formulations. Depot injections are useful for the treatment of non-compliant or partially compliant patients because they can be administered once per month.

Second-generation Antipsychotics

The second-generation antipsychotics are amisulpride, aripiprazole, clozapine, olanzapine, risperidone,

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quetiapine, ziprasidone and zotepine. Similar to first-generation antipsychotics, second-generation drugs also block dopamine receptors, but are more loosely bound to the receptors and affect serotonin and other neurotransmitter receptors as well. For example, amisulpride blocks not only dopamine-2, but also dopamine-3 receptors, and aripiprazole is a mixed dopamine agonist and antagonist.

Clozapine is the 'gold standard' of second-generation antipsychotics. It has practically no extrapyramidal side effects and is, in fact, useful in the treatment of such side effects. It is effective in the treatment of negative symptoms and depression in schizophrenia and in preventing suicidal behaviour in these patients. However, the side effects of clozapine limit its use, especially the potentially life-threatening agranulocytosis. Clozapine can only be used in patients who comply with regular blood monitoring. Clozapine has been found effective in patients who fail to improve during treatment with first-generation antipsychotics. Due to the fact that the haematological side effects restrict its use, this drug has a unique indication for 'treatment-resistant' schizophrenia.

Second-generation antipsychotics are, in general, more efficacious than first-generation antipsychotics. Their enhanced efficacy has been challenged in some earlier publications, but there is now a consensus that these drugs are more efficacious, especially with regard to the improvement in negative, depressive and cognitive symptoms of schizophrenia. The second-generation drugs decrease relapse rates and the need for hospitalisation and are more efficacious in reducing violent behaviour than the first-generation drugs.

The side effects of second-generation antipsychotics are different from those of first-generation drugs; they cause significantly fewer neurological adverse events, which contributes to the destigmatisation of psychiatric patients. However, clozapine may cause agranulocytosis, and weight gain, insulin resistance, diabetes, hypercholesterinaemia and metabolic syndrome are more frequent treatment-emergent events with second-generation than with first-generation antipsychotics. There are differences within this class of drugs, e.g. amisulpride and ziprasidone cause less weight gain, while they later increase the corrected QT interval (QTc) on electrocardiogram (ECG). Lifestyle consultation, diet and exercise have become parts of the treatment plan for schizophrenia.

Internationally accepted treatment guidelines recommend second-generation antipsychotics as first-line treatment, but their cost significantly limits access to these drugs. There is still a need for data comparing the use of low-dose first-generation antipsychotic drugs with the second-generation drugs.

The lack of availability of some formulations further limits the use of these drugs. To the author's knowledge, only three of the second-generation drugs are available in rapid-acting intramuscular form (clozapine, olanzapine and ziprasidone). Also, there is only one long-acting agent (risperidon), which has to be administered every two weeks. There is still insufficient knowledge about the use of rapid-acting second-generation intramuscular injections in the group of the most agitated and violent patients.

Length of Treatment

Internationally accepted treatment guidelines recommend different lengths of treatment after the first episode of schizophrenia and after repeated episodes. The usual recommendation is at least one year of continuous treatment after the first episode, at least five years after the second episode and long-term maintenance treatment after the third episode. Violent and suicidal behaviour are indications for longer treatment even after the first or second episode.

Educational and psychotherapeutic approaches improve insight, the recognition of early symptoms of relapse and compliance with drug treatment. These measures are of high importance in treating a chronic disorder with often decreased insight and compliance, such as schizophrenia. The recognition of early signs and symptoms of schizophrenia helps to prevent a relapse and in selected, high-risk populations it helps to start treatment as soon as the symptoms of schizophrenia are present. There is evidence that the duration of untreated psychosis is positively related to poor outcome.

Pharmacoeconomic Considerations

Schizophrenia has very high indirect costs. The disorder usually starts in the late teens or early twenties and causes lifelong disability. Repeated hospitalisation and continuous need for medical treatment after hospital discharge are the major factors responsible for the direct costs. The burden on the family, insurance and social services is enormous. Treatment with second-generation antipsychotics primarily decreases the indirect costs and improves the quality of life of the patients. The decrease in direct costs is more controversial; the cost offsets may be elsewhere, in the domain of indirect costs. Most pharmacoeconomic studies are carried out in well-developed countries; the data from these studies may be invalid in less developed countries.

Better graduate and postgraduate training of health professionals, proper budget allocation and quality assurance can help to improve services and quality of life for patients living with schizophrenia. ■