The Aims of Antipsychotic Medication
What Are They and Are They Being Achieved?

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Summary

The aims of therapy with antipsychotic medications include effective relief of symptoms without the induction of adverse effects, improved quality of life and cost effectiveness, and positive long term outcomes. However, currently available antipsychotics do not meet all of these requirements due to a number of well recognised limitations, such as a marked variability of response, induction of a wide range of adverse effects and a lack of subjective tolerability.

A lack of response to antipsychotic medications occurs in up to 30% of patients and poses a particular challenge to clinicians. The reintroduction of clozapine for the treatment of patients with refractory schizophrenia has proven useful in a good number of patients, albeit with some risk of serious agranulocytosis and at a relatively high cost.

Despite the extensive use of antipsychotics over the last 4 decades, little attention has been paid to the systematic evaluation of quality of life in patients with schizophrenia who receive medications, and in clinical trials of new agents. Similarly, there is a dearth of studies that have examined the cost effectiveness and cost utility of antipsychotics in terms of quality of life.

In general, the aim of antipsychotics of alleviating psychotic symptoms without negatively affecting the functional status of patients has not been adequately, nor consistently, achieved with currently available agents. However, with the recent acceleration in the development of new antipsychotics, it is hoped that new drugs will soon be available which will prove to be more effective in treating more symptoms of schizophrenia and will be associated with fewer, or ideally no, adverse effects.

The introduction of the first antipsychotic, chlorpromazine, in the early 1950s ushered in a new era of therapeutic optimism in the management of psychotic symptoms associated with schizophrenic, affective, organic and other psychotic conditions. Antipsychotic drugs have had an extremely profound effect on the management of schizophrenia, with these drugs becoming the mainstay of treatment in both the acute and chronic phases of the illness. However, their unrivalled reign has been challenged because of 2 factors: (i) the wide range of adverse effects associated with their use, particularly the threat of long term adverse effects such as tardive dyskinesia; and (ii) the increasing awareness of their limited usefulness in treating the broader spectrum of psychotic symptoms and disabilities. Therefore, ongoing efforts are now being directed towards the development of new antipsychotics that do not have the limitations of traditional drugs.

The aims of therapy with antipsychotic drugs are similar to those for other medications to treat psychiatric and medical disorders. Antipsychotics should provide: (i) efficacy without adverse effects;
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(ii) improved quality of life, and cost effectiveness; and (iii) positive long term outcomes.

This review discusses these aims, how they can be assessed and if they are being met by currently available drugs. Although antipsychotic medications are commonly used for the treatment of psychotic symptoms in a variety of medical, neurological and psychiatric illnesses, this review will focus mainly on schizophrenic illness.

1. Schizophrenia as a Chronic Disabling Illness

Schizophrenia is a severe and disabling mental disorder that affects approximately 1% of the population.\(^1\) Its course is generally chronic, with acute psychotic exacerbations that may require frequent hospitalisation. In spite of extensive research, the aetiology of schizophrenia remains mostly unknown. Not only does the illness cause suffering for patients and their families, but it has a major economic impact both in terms of health and social services required to treat the disorder and lost productivity due to unemployment of patients.\(^1-3\)

It is recognised that schizophrenia is likely to be a heterogeneous illness, with the implication that it may have variable aetiological, prognostic and treatment response patterns. The clinical picture, depending on the phase of illness, includes a wide array of symptoms that are generally categorised as positive (productive) and negative (deficit) [table I].

<table>
<thead>
<tr>
<th>Positive symptoms</th>
<th>Negative symptoms(^a)</th>
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<tbody>
<tr>
<td>Delusions</td>
<td>Blunted affect</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Emotional withdrawal</td>
</tr>
<tr>
<td>Conceptual disorganisation</td>
<td>Social withdrawal</td>
</tr>
<tr>
<td>Agitation</td>
<td>Lack of spontaneity</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>Poverty of speech</td>
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<tr>
<td>Hostility</td>
<td></td>
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\(^a\) Disagreement exists on what constitutes negative symptoms and whether they are primary or secondary in nature, as some may be related to positive symptoms or even medication effects.

2. Efficacy Without Adverse Effects

2.1 Efficacy

Antipsychotic medications continue to be the primary modality in the treatment of the acute phase of schizophrenic illness and in maintenance therapy for the prevention of relapse. The efficacy of antipsychotic medications in this context has been established in a large number of well controlled, double-blind studies.\(^4-7\) According to early studies by Cole et al.,\(^4,6\) almost 70% of patients with acute relapses of schizophrenia who received antipsychotics were rated as ‘much improved’ compared with only about 25% of placebo-treated patients. Similarly, maintenance antipsychotic treatment has proved effective in reducing the risk of relapse (see section 4.1)\(^7,8\)

In spite of these successes, which rival the effectiveness of accepted medications used in other chronic medical conditions, a number of limitations have been well recognised. The marked variability of response to antipsychotic medications and the wide range of adverse effects are well documented. An important proportion of patients demonstrate a lack of subjective tolerability to antipsychotics, expressed as negative subjective responses to medications. In addition, about 20 to 30% of patients with schizophrenia do not benefit from available antipsychotics.\(^7\)

2.1.1 Variability of Response to Antipsychotic Medication

It is clear that not all patients with schizophrenia benefit equally from medications, and some patients may not derive any benefits at all.\(^7,9-11\) In addition, there is concern that a subgroup of schizophrenic patients may exist who not only fail to derive any benefits from antipsychotic medications but may even deteriorate in some aspects of their functioning while receiving these agents.\(^12,13\) Such variability in response has stimulated an extensive search to identify predictors of drug response in an effort to match the medication to the patient. Table II summarises the factors that have been identified to date. This subject has been thoroughly covered in recent reviews.\(^11,14-17\) At pres-