Pharmacologic Treatment of First-Episode Schizophrenia: A Review of the Literature

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ABSTRACT

Objective: To review the evidence base for the efficacy and tolerability of antipsychotic medication for the treatment of the first episode of schizophrenia.

Data Source: MEDLINE databases were searched for published articles in English over the last 25 years, from January 1986 to January 2011, on choice of antipsychotic treatment for the first episode of schizophrenia, with an emphasis on efficacy and tolerability of antipsychotic drugs in the acute phase of psychotic illness.

Study Selection: The keywords *antipsychotic drugs* and *schizophrenia* were used in combination with *drug treatment*, *pharmacologic treatment*, *efficacy*, and *tolerability* in addition to *atypical antipsychotics*, *first-generation antipsychotics*, *second-generation antipsychotics*, *first-episode psychosis*, and *acute psychotic episode*.

Data Synthesis: At present, there is no convincing evidence to guide clinicians in choosing a single first-line antipsychotic that is effective in treating the positive and negative symptoms of the first episode of schizophrenia. Even though second-generation antipsychotic drugs offer potential benefits in terms of less extrapyramidal side effects and some benefits in treating negative, affective, and cognitive symptoms, these drugs are not without their own side effects.

Conclusions: With the introduction of a number of second-generation antipsychotic drugs there have been significant advances in antipsychotic drug treatment over the last decade. Despite these advances, there are still a number of limitations in continued use of some antipsychotic medications due to their efficacy and tolerability issues in the acute and early maintenance phases of psychosis. Active research in this area would provide more promising results of improved efficacy and tolerability of antipsychotic medication.

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Exciting advances in neuroimaging techniques over the last 3 decades have allowed sophisticated examination of brain structure and functioning. Functional magnetic resonance imaging can accurately determine cerebral blood flow changes in localized regions of the brain during performance of cognitive tasks. Imaging methods such as positron emission tomography (PET) and single-photon emission computed tomography allow for examination of brain metabolism and receptor occupancy. Over the last decade, these techniques have contributed greatly to the evolving understanding of the human neurobiology of schizophrenia.

The brain neurotransmitter abnormalities found in schizophrenia are the basis for development of antipsychotic medication for psychosis. The primary neurotransmitters implicated in the pathogenesis of psychosis are dopamine and serotonin.

The brain neurotransmitter dopamine is most often linked to schizophrenia. PET studies examining amphetamine-induced dopamine release reveal excessive levels of subcortical dopamine synthesis in the striatum of patients, both at the onset of schizophrenia and in drug-naive patients.[1] Increased caudate dopamine-2 (D_2) receptor availability has been found in unaffected monozygotic cotwins of schizophrenia probands. Caudate dopamine receptor up-regulation is a trait marker related to schizophrenia vulnerability.[2] Hypofrontality has been widely studied in schizophrenia since the early 1970s. This hypofunctioning is clearly seen when subjects are performing tasks, such as the Wisconsin card sorting test, that require activation of the frontal lobes. Functional imaging studies report reduced D_1 receptor binding in the dorsolateral prefrontal cortex of drug-naive schizophrenia patients.[3] Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia.[4]

There are currently 5 types of dopamine receptors identified in the human nervous system. These receptors are grouped into 2 families: the D_1-like family includes D_1 and D_5 and the D_2-like family includes D_2, D_3, and D_4. The original dopamine hypothesis was based on the assumption that dopamine only innervated subcortical regions and that these regions were overstimulated by excessive dopamine transmission. The affinity of antipsychotic to subcortical D_2 receptors was found to be proportionate to the clinical potency of the antipsychotic.[5] Later, it was postulated that psychosis is a state of aberrant salience, with dopamine mediating the salience of environmental events and internal representations. Hyperdopaminergic states at "brain" levels of description and analysis lead to an aberrant assignment of salience to the elements of one's experience at a "mind" level. Delusions are an effort by the patient to make sense of these aberrant salient experiences, whereas hallucinations are a direct experience of the aberrant salience of internal representations.[6] There are many other (potentially competing) theories and biological/cognitive mechanisms for delusions. The most recent evidence suggests that delusions arise in schizophrenia and in other disorders and can be accounted for by a combination of dysregulated firing in ascending midbrain dopamine neurons and reasoning bias.[7]

The serotonergic hypothesis stemmed from the finding by Woolley and Shaw[8] in 1954 that the hallucinogen lysergic acid diethylamide (LSD) acted

via serotonin. Several distinct serotonin receptors have been identified and all are G protein–coupled receptors, with the exception of the serotonin-3 (5-HT_3) receptor, which is a ligand-gated Na^+/K^+ channel. The functional interaction of 5-HT and dopaminergic systems is such that blocking 5-HT_{2A} receptors enhances dopaminergic transmission. All second-generation antipsychotics have a higher affinity for the 5-HT_{2A} receptor than for the D_2 receptors, and they occupy cortical 5-HT_{2A} receptors almost completely at clinically relevant doses.[9]

γ-Aminobutyric acid (GABA) appears to have a regulatory role on dopaminergic function. It is possible that in psychosis there is reduction in GABAergic function that leads to increased dopamine concentration and the production of psychotic symptoms.[10]

Glutamate is a major excitatory neurotransmitter in the central nervous system, acting through both ligand-gated ion channels (ionotropic receptors) and G-protein–coupled receptors (metabotropic receptors). The ionotropic receptors include *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainite. The metabotropic receptors are activated via G proteins. *GRM3* encodes a metabotropic glutamate receptor responsible for modulating synaptic glutamate and is a candidate gene for schizophrenia. Psychotic symptoms can be produced by decreased glutamatergic function at NMDA receptors. For example, phencyclidine and ketamine, which are antagonists of the NMDA receptor, increase dopamine release in the mesolimbic system and exacerbate psychotic symptoms in schizophrenia, producing a quasipsychotic state in normal controls resembling schizophrenia to some degree.[11] Psychotic symptoms can also be produced by increased glutamatergic function at AMPA and kainite receptors. For example, LSD activates 5-HT_{2A} receptors that in turn increase glutamate release. Deficiency of glutamate transmission is postulated to lead to diminished mesocortical dopamine release and hence to the core negative symptoms and cognitive deficits in schizophrenia.

Acetylcholine is a neurotransmitter widely distributed in the brain with actions in the neocortex, hippocampus, and striatum and at midbrain dopamine neurons. Acetylcholine acts through the ligand-gated nicotinic and G protein–coupled muscarinic receptors. There is evidence for decreased numbers of both muscarinic and nicotinic receptors in schizophrenia. Moreover, acetylcholine can modulate the dopamine transmission in the striatum and in the cortex. Cortical deficits in dopamine have been postulated to contribute to negative and cognitive symptoms. Overactivity of the striatum due to dopamine dysregulation may contribute to positive symptoms.[12]

Alterations in the cannabinoid system in the brain have been reported in several clinical studies of patients with schizophrenia. Recent studies suggest that cannabinoids such as cannabidiol and SR141716, a potent and selective cannabinoid receptor 1 antagonist, have a pharmacologic profile similar to that of atypical antipsychotic drugs.[13] Disruption related to these other neurotransmitter pathways is known in schizophrenia (GABA, glutamate, acetylcholine, and endocannabinoids); however, the involvement appears indirect, with little clear therapeutic relevance.

This review examines the evidence base for the efficacy and tolerability of antipsychotic medication, both first and second generation, for the treatment of the acute and maintenance phase of the first episode of schizophrenia. The psychopharmacologic properties of various antipsychotic drugs, including their classification and side effect profiles, as well as nonpharmacologic treatment options for schizophrenia, drug treatment of resistant schizophrenia, and treatment of comorbid conditions, are also discussed.

METHOD

MEDLINE databases were searched for published articles in English over the last 25 years, from January 1986 to January 2011, on choice of antipsychotic treatment for the first episode of schizophrenia with an emphasis on efficacy and tolerability of antipsychotic drugs in the acute phase of psychotic illness. The keywords *antipsychotic drugs* and *schizophrenia* were used in combination with *drug treatment*, *pharmacologic treatment*, *efficacy*, and *tolerability* in addition to *atypical antipsychotics*, *first-generation antipsychotics*, *second-generation antipsychotics*, *first-episode psychosis*, and *acute psychotic episode*. Reference lists of all relevant articles were scrutinized for more citations.

It is essential to have an up-to-date knowledge of various antipsychotic drugs in use and their side effect profiles. Before discussing the evidence base for antipsychotic treatment for first-episode schizophrenia, the relevant literature on the generally accepted classification of antipsychotic drugs and their short-term and long-term adverse effects is presented.

CLASSIFICATION OF ATYPICAL ANTIPSYCHOTIC DRUGS

Second-generation antipsychotic drugs have a diverse pharmacology, but, currently, 2 groups can be discerned.

1. Substituted benzamide such as amisulpride is a pure D_2 and D_3 receptor antagonist that is less likely to cause extrapyramidal side effects and lacks sedative and anticholinergic properties. However, it can cause high prolactin levels.
2. The 5-HT_2 D_2 receptor antagonists are the second-generation antipsychotic drugs that possess 5-HT_2 antagonist action. Risperidone is a potent antagonist at both 5-HT_2 receptors and D_2 receptors. Risperidone also possesses α_1-adrenoceptor–blocking properties that can cause hypotension. Olanzapine is a slightly weaker D_2 receptor antagonist than risperidone but has anticholinergic and H_1 receptor–blocking activity, giving it strong sedating effects. Quetiapine has modest 5-HT_2 receptor antagonist effects with even weaker D_2

Table 1. Side Effects of Atypical Antipsychotic Drugs (second-generation antipsychotics)

Drug	Dopamine (D)/ Serotonin (5-HT)	General Side Effects	Systemic Side Effects
Amisulpride	D_2/D_3 antagonism	Insomnia, anxiety, agitation, dry mouth, nausea, constipation	Bradycardia, QTc prolongation (rare), weight gain (mild), hyperprolactinemia
Clozapine	$D_4 > D_1 > D_2$ 5-HT_{2A}, 5-HT_{2C}	Fatigue, drowsiness, dizziness, headache, tremor, anorexia, nausea, vomiting, excessive salivation, sweating, dry mouth, constipation	Agranulocytosis, myocarditis and myopathy, tachycardia, postural hypotension, weight gain, ileus, urinary retention, seizures, diabetes
Olanzapine	5-$HT_2 > D_2 > D_1$	Fatigue, drowsiness, dizziness, increased appetite, edema	Hypotension, QTc prolongation, bradycardia, raised triglycerides, diabetes, hyperprolactinemia
Quetiapine	5-$HT_2 > D_2$	Drowsiness, dizziness, headache, blurred vision, dry mouth, constipation	Tachycardia, hypertension, postural hypotension, QTc prolongation, raised triglycerides, hyperprolactinemia, abnormal liver function, leucopenia, neutropenia, seizures
Risperidone	5-$HT_2 > D_2$	Insomnia, agitation, anxiety, headache, tremor, impaired concentration, dry mouth	Hyperprolactinemia, sexual dysfunction, blood disorders, QTc prolongation
Aripiprazole	5-HT_{1A}/D_2 partial agonist, 5-HT_{2A} antagonist	Fatigue, drowsiness, headache, tremor, agitation, insomnia, nausea, vomiting	Hypertension, bradycardia, seizures

receptor antagonist effects. Quetiapine has a very low propensity to produce movement disorders. Aripiprazole is a partial dopamine agonist that also has 5-HT_2 receptor–blocking properties. Aripiprazole is less likely to cause weight gain or extrapyramidal side effects. Clozapine is the prototypical atypical antipsychotic drug.[14] Clozapine is a weak D_2 receptor antagonist but has a high affinity for 5-HT_2 receptors. It also binds to other receptors such as histamine H_1 and α_1-adrenergic and muscarinic-cholinergic receptors.[15] Gelder et al[16] provides a review of these second-generation antipsychotic drugs.

Adverse Effects

Short-term adverse effects. Table 1 summarizes the common side effects of atypical antipsychotic drugs. Gelder et al[16] provides a review of common side effects. Most second-generation antipsychotics are more potent 5-HT_2 and D_4 antagonists than D_2 antagonists. This finding led to the current hypothesis that the relatively low affinity of the D_2 receptors leads to the atypical drug effect.[17] The 5-HT_{2A} antagonism at moderate doses seems to protect from extrapyramidal symptoms; however, higher doses of atypical antipsychotics such as risperidone and olanzapine can lead to striatal D_2 receptor occupancies associated with higher incidence of extrapyramidal symptoms.

Long-term adverse effects: metabolic syndrome and its consequences. Metabolic syndrome is a state of hyperinsulinemia, low glucose tolerance, dyslipidemia, hypertension, and obesity. Insulin resistance is the central characteristic, leading to the increased risk of mortality from coronary heart disease.[18] Clozapine and olanzapine can induce insulin resistance independent of the induction of weight gain.[19] In 1 study,[20] one-third of patients treated with clozapine followed over a 5-year period developed type 2 diabetes, of which two-thirds required oral hypoglycemic or insulin and one-third was managed with dietary interventions. A large American cross-sectional study[21] suggested that prevalence of diabetes in those patients prescribed any atypical antipsychotic (not risperidone) was significantly increased by 9% compared to those who received typical neuroleptics. A more recent meta-analysis[22] reported that the relative risk of diabetes in patients with schizophrenia prescribed a second-generation versus first-generation antipsychotic was 1.32. The authors concluded that there is tentative evidence that second-generation antipsychotics are associated with a small risk for diabetes and that regardless of type of antipsychotic used, screening for diabetes in all people with schizophrenia should be routine. [22]

Physical health monitoring. There is no clear consensus on diabetes monitoring for those receiving antipsychotics.[23] Ideally, all patients should have an oral glucose tolerance test performed, as this is the most sensitive testing method.[24] A fasting plasma glucose test is less sensitive but is recommended.[25] Random plasma glucose in conjunction with glycosylated hemoglobin may also be used.[26] Subsequent monitoring should be based on individual risk, eg, weight gain, family history of diabetes, and lipid abnormalities. The absolute minimum monitoring requirement is yearly testing for all patients, and all patients should have their lipid levels measured at baseline.[26] Those patients prescribed clozapine, olanzapine, quetiapine, or phenothiazines should have their serum lipid levels measured every 3 months for the first year of treatment, and those taking other antipsychotics should have their lipid levels measured after 3 months and then annually thereafter.[26]

Many antipsychotic drugs are associated with electrocardiogram (ECG) changes, and it is probable that certain drugs are causally linked to serious ventricular arrhythmia and sudden cardiac death.[27] Overall risk is clearly dose related; however, it remains low. ECG monitoring is essential for all patients taking antipsychotics. A measure of the QTc interval should be made in all patients at admission to and before discharge from inpatient units and yearly thereafter.[27] The need for ECG monitoring can be minimized by prescribing drugs with the lowest effect on the QT interval at the minimum effective dose and by

avoiding polypharmacy with other QT-prolonging drugs and hepatic enzyme inhibitors.[27]

ANTIPSYCHOTIC TREATMENT FOR FIRST-EPISODE SCHIZOPHRENIA

Choice of Antipsychotic Drugs

The National Institute for Clinical Excellence (NICE)[28] guidelines recommend the use of oral antipsychotic medication for newly diagnosed schizophrenia. Treatment with antipsychotics should be considered as an explicit individual therapeutic trial that includes 4 to 6 weeks of optimal dosage. The NICE guidelines recommend regular and systematic monitoring and recording of efficacy, side effects of treatment, adherence, and physical health throughout this treatment period.[28] In general, atypical (second generation) antipsychotics are associated with fewer extrapyramidal symptoms than typical antipsychotics (first generation), and some do not raise prolactin levels. With the exception of clozapine, for which there was robust evidence for use in people who do not respond adequately to other antipsychotics, NICE was unable to make a recommendation for a preference of 1 antipsychotic over another due to lack of evidence to distinguish antipsychotics on efficacy grounds.[28] At present, there is no convincing evidence that second-generation antipsychotics (excluding clozapine) are more effective than first-generation drugs in treating the positive and negative symptoms of first-episode psychosis.[29–31]

What Dose?

The NICE guidelines recommended that doses should be gradually titrated up to an equivalent of 300–900 mg of chlorpromazine daily, as most patients will respond at this range.[28] Patients should be treated with the minimum effective dose (ie, start with a dose at the lower end of the licensed range and titrate upward slowly within the dose range). Many patients with first-episode psychosis will respond at the bottom end or even below this range. A PET study demonstrated that antipsychotic response is optimized at a threshold of approximately 65% to 70% of D_2 occupancy, whereas exceeding 80% leads to a substantial increase in the risk of extrapyramidal symptoms.[32] This threshold allows greater precision in calculation of approximate dose equivalents (mg) for both typical and atypical antipsychotics on the basis of D_2 occupancy. Using 2 mg of haloperidol as a comparison, the comparative dose equivalents are olanzapine 10 mg and risperidone 2.5–3.0 mg. The equivalent doses for clozapine and quetiapine are difficult to estimate, as the D_2 occupancy of these drugs is markedly influenced by their fast dissociation values.[33]

How Long Should Treatment Continue?

It is not clear for how long patients with first-episode psychosis should continue maintenance antipsychotic medication. A placebo-controlled study found that when no prophylactic treatment is given, 57% of first-episode patients have a relapse at 1 year.[34] Another study in first-episode patients found that discontinuing antipsychotic medication increased the risk of relapse 5-fold.[35] Consensus guidelines recommend 1 to 2 years of prophylaxis for all people diagnosed with schizophrenia.[36]

The decision to stop antipsychotic medication requires a thorough risk-benefit analysis for each patient. Withdrawal after long-term treatment should be gradual and closely monitored. It is vital that patients, caregivers, and health care professionals are aware of the early signs of relapse and how to access help.[28] Once prescribed, the clinician should monitor the mental state of the patient and review clinical indications, frequency of administration, therapeutic benefits, and side effects each week or as appropriate. The NICE guidelines[28] also recommend recording of the rationale for continuing, changing, or stopping medication and the effects of such changes. For floridly psychotic patients with behavioral disturbance and agitation not adequately controlled, an adjuvant such as lorazepam may be added to the treatment regimen, and its side effects should be monitored and treated appropriately. The NICE guidelines also indicate the routine use of prophylactic antiparkinsonian drugs such as 5–10 mg of intramuscular procyclidine, given at the same time or shortly after intramuscular haloperidol.[28]

What If the Patient Fails to Respond?

Treatment resistance: clozapine use and augmentation. Clozapine has been in use since 1960 and was withdrawn after an association with neutropenia (3%) and agranulocytosis (0.8%) was found.[37] The study by Kane et al[14] in the late 1980s demonstrated that clozapine was more effective than conventional antipsychotics, and it was reintroduced in the United Kingdom in the early 1990s.

The incidence of treatment resistance (failure to respond to antipsychotic therapy) is around 10% to 30%.[38] Factors that may contribute to treatment resistance include nonadherence (noncompliance) to treatment, comorbid conditions, and medication side effects. NICE recommends that clozapine be used for schizophrenia resistant to another atypical antipsychotic.[28] However, before initiating clozapine therapy, patients should be assessed to reevaluate the diagnosis, considering organic contributions to the diagnosis, noncompliance, and comorbidity. Studies have shown that 30% of patients previously refractory to treatment respond after 6 weeks of treatment with clozapine, a further 20% respond after 3 months, and an additional 10% to 20% respond after 6 months.[39] Many of the side effects of clozapine are dose dependent and associated with speed of titration. To minimize these problems, it is important to start treatment at a low dose and to increase the dosage slowly.[28]

Most clinicians are now more concerned with managing clozapine-resistant patients. Switching from clozapine to a previously untried atypical antipsychotic (eg, olanzapine, risperidone, quetiapine) might be of benefit in partial treatment resistance. In more difficult cases, augmentation of clozapine with benzamides (sulpiride, amisulpride) and antiepileptics (lamotrigine) shows some success.[40–42] It is recommended that all augmentation attempts be carefully

monitored and, if no clear benefits are forthcoming, abandoned after 3 to 6 months.[27] Always consider the use of mood stabilizers and/or antidepressants, especially when mood disturbance is thought to be contributing to symptoms. Barnes et al[43] provides a review of treatment-resistant schizophrenia unresponsive to clozapine.

Therapies adjunct to pharmacologic treatment. Psychoeducation and family therapy are currently advocated in the management of psychosis for patients who live with or are in close contact with their family.[28,44] Family interventions reduce relapse rates in psychosis. Cognitive-behavioral therapy (CBT) improves positive symptoms, but effects on relapse rates are not well established. A recent study on CBT and family intervention[45] concluded that the generic CBT for psychosis is not indicated for routine relapse prevention in people recovering from a recent relapse of psychosis and should be reserved for those with distressing medication-unresponsive positive symptoms. A range of psychological treatments for cognitive deficits in psychosis has been studied. One of the most extensively tested is cognitive remediation therapy. However, results are unclear.[46,47] Compliance therapy can be an adjunct to pharmacologic treatment by providing information on medication and using motivational interview and cognitive approaches to psychotic symptoms.[47] A randomized controlled trial of compliance therapy conducted by Kemp et al[48] found that compliance therapy could lead to improvement in insight and adherence to medication.

Treatment of Comorbidity

Substance misuse. Comorbid substance use disorders, mostly involving alcohol, cannabis, or cocaine, are associated with increased morbidity and mortality. High prevalence rates of substance misuse, in particular for cannabis, have been found in first-episode psychosis.[49] Heavy substance use appears to be independently associated with poorer symptomatic and functional outcome in young patients with first-episode psychosis.[50] Presence of these comorbid substance use disorders may negatively influence response to antipsychotic medications.[51] Psychotic patients with comorbid substance misuse should engage with drug and alcohol teams early in the course of illness. There is evidence for the therapeutic effects of clozapine in improving substance misuse in patients with schizophrenia.[52]

Depressive disorders. The majority of patients with schizophrenia also experience significant depressive features at some point. Depressive features range from 7% to 75%, and a modal rate of 25% has been reported in schizophrenia.[53] Depression can be an integral part of the illness, antipsychotic induced, or a postpsychotic depression as patients gain insight and become demoralized from learning about the illness.

Depression in psychosis is associated with impaired functioning, high rate of relapse or rehospitalization, and suicide. Treatment studies with antipsychotics have shown that some of the second-generation antipsychotics such as olanzapine appear to have a greater antidepressant effect than the first-generation drugs, and it was found that depressive symptoms tend to improve in parallel with improvements in psychotic symptoms.[54] The NICE guidelines recommend these drugs for the treatment of depressive symptoms.[28] Most clinicians prescribe an antidepressant, usually a selective serotonin reuptake inhibitor, when they observe depression in patients with psychosis, but it is important to note that, as yet, there have been no reported randomized controlled trials in this area. It is also important that psychological approaches be tried before medication.[55]

Anxiety disorders. Anxiety disorders, particularly obsessive-compulsive disorder, panic disorder, and social anxiety disorder, seem to be comorbid with early psychosis. Social anxiety disorder might negatively impact the course of the illness.[44] Early recognition and treatment of these comorbid disorders could have an impact on long-term outcomes of psychosis.

DISCUSSION

There are a number of antipsychotics, both first generation and second generation, available to treat the first episode of psychosis in schizophrenia. Choosing an antipsychotic with the best efficacy and tolerability is still a challenge for clinicians. The selection of a specific antipsychotic agent should be based on efficacy, side effect profile, history of prior response or (nonresponse) to a specific drug, or history of response of a family member to a specific antipsychotic. It is also known that noncompliance or suboptimal treatment adherence affects up to 80% of patients with psychosis.[56] It is vital to ensure treatment compliance, since a large proportion of patients are noncompliant or partially compliant.

NICE has updated its clinical guidelines on initiating treatment of first-episode schizophrenia.[28] With regard to choice of antipsychotic drug, the updated version does not recommend use of any particular drug or group of drugs. The previous NICE guidelines on schizophrenia recommended second-generation (atypical) antipsychotics as first-line treatment.[57] This recommendation was based on the assumption that second-generation antipsychotics would have lower extrapyramidal side effects. But further evaluation by NICE of recent trials revealed that most trials were of short duration and were not designed to study the side effects prospectively. In the updated guideline,[28] it is suggested that choosing the best antipsychotic for an individual is more appropriate than the drug group. However, NICE has not provided any information on side effect profiles of individual antipsychotics to assist clinicians in choosing the most appropriate drug for an individual.

Meta-analyses of acute treatment trials differ in conclusions as to whether second-generation antipsychotics have superior efficacy and tolerability to first-generation antipsychotics. For example, Geddes et al[29] carried out a meta-analysis and concluded that, using 6–12 mg of haloperidol or its equivalent as a comparator, there was no clear evidence that second-generation antipsychotics were more effective or better tolerated than first-generation

antipsychotics. The authors therefore recommended the use of typical antipsychotics in the first instance, unless the patient has not responded to this class of drugs or had unacceptable side effects. A subsequent meta-analysis by Davis et al[58] reported significant efficacy for several atypical antipsychotics and recommended the use of olanzapine, risperidone, and amisulpride as first-line antipsychotics. In a more recent randomized controlled trial, Kahn et al[59] suggested that clinically meaningful antipsychotic treatment is achievable in first-episode psychosis patients with several of the second-generation antipsychotics. The results of this European First Episode Schizophrenia Trial study indicate that patients continued on treatment with second-generation antipsychotics for longer periods than low-dose haloperidol and more patients discontinued treatment due to lack of efficacy than for side effects.[59]

The evidence for superior efficacy of second-generation compared to first-generation antipsychotics in long-term maintenance treatment of psychosis is still unclear. In a systematic review, Leucht et al[60] confirmed that second-generation antipsychotics are more effective compared to placebo in preventing relapses and produce modestly low rates of relapse compared to first-generation antipsychotics. In a later large long-term trial, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study compared several second-generation antipsychotics such as olanzapine, quetiapine, risperidone, and ziprasidone with the first-generation drug perphenazine.[31] In a total of 1,493 patients, 74% discontinued their treatment due to inefficacy, intolerable side effects, or other reasons. The time to discontinuation was longest with the olanzapine group, but this drug was associated with significant weight gain and metabolic effects. The efficacy of perphenazine was similar to that of quetiapine, risperidone, and ziprasidone.[31]

The CATIE study was defended by The Cost Utility of Latest Antipsychotic Drugs in Schizophrenia Study.[30] In this pragmatic multicenter study in the United Kingdom, the authors concluded that, in people with schizophrenia whose drug treatment needs to be changed for clinical reasons, there is no disadvantage in terms of quality of life, symptoms, or associated costs of care across 1 year in commencing treatment with first-generation rather than nonclozapine second-generation antipsychotic drugs in patients with schizophrenia whose medication is changed because of intolerance or inadequate response.[30] See Owens[61] for a review of the CATIE findings.

Although there are a number of comparative studies on the efficacy and tolerability of first- and second-generation antipsychotics, there is still no convincing evidence to support superior efficacy of either of class of drug in treating a first episode of schizophrenia. With the introduction of newer antipsychotics, there has been significant reduction in the use of first-generation antipsychotic drugs and subsequent reduction in morbidity due to their side effects. But with the increase in use of second-generation antipsychotic drugs, there is now accumulating evidence on their long-term side effects. With the exception of clozapine, there is still a lack of evidence to support use of one particular second-generation antipsychotic over another as having superior efficacy in treating psychosis. In other words, all of the currently available second-generation antipsychotics are more similar in efficacy but differ in their side effect profile. Further clinical trials are need in this area to explore the benefits of potential newer agents that are least likely to cause adverse effects but at the same time provide superior efficacy compared to currently available drugs.

Future

Future developments may include a new generation of antipsychotics acting as agonists at the metabotropic glutamate receptors. Group II metabotropic glutamate receptors are autoreceptors that inhibit release of glutamate and regulate other neurotransmitters and have been implicated in schizophrenia.[62] Most recent trials using cholinergic agonists have produced promising results as novel treatments for schizophrenia, targeting its negative and cognitive symptoms.[11]

Pharmacogenetic studies may also help in predicting response to a particular drug by analyzing the allelic variations for individual receptors that correlate with response. Antipsychotic drugs are known to show marked interindividual variation in therapeutic response, with some individuals failing to respond even to high doses, and others showing side effects at doses well below the usual therapeutic range.[63]

CONCLUSION

Despite the advances in the psychopharmacology of antipsychotics since the early 1950s, there are still gaps in our knowledge and clinical practice. Even though second-generation antipsychotics offer benefits in terms of less extrapyramidal symptoms, these medications are not without their own side effects. Another limitation of drug treatment is that there are still 40% to 50% of patients with schizophrenia who do not have an optimal response to antipsychotics and some 20% who become resistant to all forms of treatment including clozapine.[64]

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), ketamine (Ketalar and others), lamotrigine (Lamictal and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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