REVIEW ARTICLE

Treatment of psychosis: 30 years of progress

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SUMMARY

Background: Thirty years ago, psychiatrists had only a few choices of old neuroleptics available to them, currently defined as conventional or typical antipsychotics, as a result schizophrenics had to suffer the severe extra pyramidal side effects. Nowadays, new treatments are more ambitious, aiming not only to improve psychotic symptoms, but also quality of life and social reinsertion. Our objective is to briefly but critically review the advances in the treatment of schizophrenia with antipsychotics in the past 30 years. We conclude that conventional antipsychotics still have a place when just the cost of treatment, a key factor in poor regions, is considered. The atypical antipsychotic drugs are a class of agents that have become the most widely used to treat a variety of psychoses because of their superiority with regard to extra pyramidal symptoms. We can envisage different therapeutic strategies in the future, each uniquely targeting a different dimension of schizophrenia, be it positive, negative, cognitive or affective symptoms.

Keywords: atypical antipsychotic, pharmacology, psychosis, schizophrenia, treatment

INTRODUCTION

In 2005, the Journal of Clinical Pharmacy and Therapeutics marked its 30th year. Of all the outstanding advances in medical practice over this period, one of the most impressive has taken place in the field of diagnosis and treatment of schizophrenia. Thirty years ago, psychiatrists had few neuroleptics available to them. These were all compounds, today known as conventional antipsychotics, and all were liable to cause severe extra pyramidal side-effects (EPS). Nowadays, new treatments are more ambitious, aiming not only to improve psychotic symptoms, but also quality of life and social reinsertion. We briefly but critically outline the advances in diagnosis and treatment of schizophrenia, from the mid 1970s up to the present.

DIAGNOSIS OF SCHIZOPHRENIA

Up until the early 1970s, schizophrenia diagnoses remained debatable. The lack of uniform diagnostic criteria led to relative rates of schizophrenia being very different, for example, in New York and London, as demonstrated in an important study which became known as the United States–United Kingdom Study (1). A recent study using standardized criteria (2) showed similar prevalence of schizophrenia and mood disorders across the Atlantic (3).

The DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition) (4) incorporated criteria developed by Feighner et al. (5) – the Washington University Criteria, which required the presence of symptoms for at least 6 months. Such criteria established schizophrenia as a chronic and severe disorder, with few patients achieving full recovery (3). Currently, the DSM is in its 4th version (6) and its diagnostic criteria are used worldwide, standardizing the diagnosis of schizophrenia and allowing results of clinical trials to be compared.

Advances in two other fields have led to great improvement in our understanding and diagnosis of schizophrenia: neuroimaging studies and genetics. At the time the Journal was launched,
studying the living brain was becoming safe with the introduction of imaging techniques, enabling symptoms and brain structures to be correlated. In 1980, Crow (7) made a distinction between schizophrenia type I, with more positive symptoms correlated with increased dopamine (DA) type 2 receptors and type II schizophrenia, with more negative symptoms correlated with an enlarged ventricle and a diminished cerebral cortex. Positive symptoms include unusual experiences such as perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions). Negative symptoms comprise a lack of ordinary mental activities such as thoughts and motivation. Studies using magnetic resonance imaging (MRI) have demonstrated structural and functional brain abnormalities, predominantly involving frontal and temporal lobes, and in most cases already present at the onset of illness, which usually manifests during adolescence or young adulthood.

Early diagnosis began to play an important role in the strategy of treatment, and there was a growing interest in the length of time between symptoms’ first appearance in individuals and the time they first received treatment, and whether this period of untreated psychosis was associated with illness outcome. Perkins et al. (8) found that the longer the patient remained untreated, the worse was the response to antipsychotic treatment and severity of negative symptoms on first treatment. Another promising area is the use of MRI to monitor and define partial and full resistance to medication, as several abnormal brain changes have been recently correlated with the antipsychotic treatment (9).

Finally, recent molecular genetic studies have identified several strong candidates for susceptibility genes, such as the gene for dysbindin (DTNBP1), the gene for neuregulin-1 (NRG1) and the locus G72/G30 (10). The clinical implication of these findings are not yet evident, and most of the genetic findings to date lack diagnostic specificity, although these genes are set to open up new vistas for neurobiological research.

TYPICAL VS. ATYPICAL ANTIPSYCHOTICS

A number of typical, conventional, antipsychotics have been developed since chlorpromazine was discovered in the early 1950s. They have been widely used and shown to be effective in the treatment of positive symptoms of schizophrenia and related psychoses, as well as in preventing psychotic relapses (11). However, crucial limitations such as persistent symptoms in 25–60% of the patients (labelled either treatment refractory, or partial responders), only modest improvement of negative and cognitive symptoms and a variety of side effects both acute (e.g. EPS) and chronic [e.g. tardive dyskinesia (TD)] represent a major drawback of these drugs (12). Nevertheless, research interest lagged behind these clinical observations and it took almost 20 years to ‘jump-start’ focused research to delineate these conditions and identify their determinants. All studies during this period were mainly clinical and descriptive in nature. By the mid-1980s, all that could be accomplished in research had already been achieved, within the constraints of research methodologies available at the time.

For many years, it was widely accepted that any effective drugs for schizophrenia should also induce EPS, where the term ‘neuroleptic’ was originally used to describe such neurological side-effects. However, adverse effects, such as movement disorders and sedation, are problematic and can result in non-compliance with medication. Positive symptoms, such as delusions, hallucinations and thought disorders are more often in acute phases of the illness than are negative symptoms, such as poverty of speech, lack of motivation, apathy and inability to express emotions (13). Negative symptoms, however, are probably more disabling and may not respond as well to typical antipsychotic drugs.

Atypical antipsychotic drugs, by definition, differ from typical antipsychotic agents in producing significantly fewer EPS and carrying a lower risk of TD in vulnerable clinical populations at doses that result in comparable control of psychosis. The atypical drugs differ from the typicals in their mechanism of action, but not all share the same mechanism. Many, but not all, atypicals have been found to improve cognitive function, which could be their most important advantage with regard to efficacy. Clozapine, the prototype of these agents, has been found to improve delusions and hallucinations in patients who fail to respond to other antipsychotic drugs, and to reduce the risk of suicide. These agents have been found to increase
cortical DA and acetylcholine release, as well as to have a variety of effects on the glutamatergic system not shared by the typical agents. Effects on neuronal survival and plasticity, together with decreased neurotoxicity, might also contribute to their clinical advantage over typical neuroleptic drugs (14).

The term ‘atypical’ was first introduced to describe clozapine, since its properties were found to be different from the older, conventional, or typical neuroleptics (15). The term ‘atypical’ was then accepted as including the characteristics common to those antipsychotic drugs developed more recently, including: (a) absence of hyperprolactinemia; (b) greater efficacy in treating positive and negative symptoms and symptoms of disorganization; and (c) absence of TD or dystonia after being administered chronically (16, 17). However, only clozapine seems to fulfil such criteria (18). If we broaden the definition of the term ‘atypical’ to encompass the drugs that have at least equal antipsychotic activity compared to conventional neuroleptics and produce no or fewer EPS, several second-generation antipsychotics (risperidone, olanzapine, ziprasidone, quetiapine, sertindol and aripiprazol) possess such properties (19).

**ATYPICAL ANTIPSYCHOTICS**

The term atypical has been used too promiscuously for it to have a robust scientific meaning. Yet, the remarkable frequency of its use, coupled with the failure of more scientifically reliable terms to replace it, suggests that the term conveys a valuable meaning. At least in clinical circles most would agree that clozapine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone and aripiprazol and amisulpride, and it is now understood that this exception may largely be attributed to these drugs having a higher peripheral/central distribution ratio, thereby leading to excessive DA blockade in the pituitary that lies outside the blood–brain barrier (21).

‘Atypical’ is a term widely used to describe some antipsychotics with specific characteristics such as minimal risk of acute and chronic movement disorders and less sedation (22). The atypical antipsychotic drugs are also thought to be more effective than conventional drugs in the treatment of negative symptoms in schizophrenia, although this has not yet been adequately established (23). At present, new antipsychotics are routinely investigated for their possible effect on negative symptoms. In spite of their better tolerability profile, the clinical antipsychotic trials of intervention effectiveness (CATIE) (24) showed a high dropout rate with atypical antipsychotics because of either inefficacy or intolerable side-effects. In this trial, the conventional antipsychotic perphenazine appeared similar to quetiapine, risperidone and ziprasidone in terms of efficacy, but perphenazine had more discontinuations because of EPS.

In the topics below, clozapine and the more recent atypical antipsychotics (risperidone, olanzapine, quetiapine, sertindol and aripiprazol) are reviewed.

**RECEPTOR PHARMACOLOGY OF ANTIPSYCHOTICS**

Two important studies were published in 1976 related to receptor pharmacology of the antipsychotic drugs. The studies by Creese et al. (25) and by Seeman et al. (26) confirmed the observation of Carlsson and Lindqvist (27) that neuroleptics altered the turnover of DA, suggesting that they work by blocking DA receptors and proposing the DA hypothesis that was to guide neurobiological research of schizophrenia for the 30 years that followed (28).

Serotonin (5-HT)-receptor-based mechanisms have been postulated to play a critical role in the action of the new generation of antipsychotic drugs, usually referred to as atypical antipsychotics, because of their ability to achieve an antipsychotic effect with lower rates of EPS compared to first-generation antipsychotic drug (APDs) such as
haloperidol. Specifically, it has been proposed by Meltzer et al. (29) that potent 5-HT2A receptor antagonism, together with weak D2 receptor antagonism are the principal pharmacological features that differentiate clozapine and other apparent atypical antipsychotics from first-generation typical antipsychotics. This hypothesis is consistent with the atypical features of quetiapine, olanzapine, risperidone and ziprasidone, which are the most common treatments for schizophrenia in the USA and many other countries. A large number of compounds in various stages of development also share these features. Subsequent research has shown that 5-HT1A agonism may be an important consequence of 5-HT2A antagonism and that substitution of 5-HT1A agonism for 5-HT2A antagonism may also produce an atypical antipsychotic drug when coupled with weak D2 antagonism. Aripiprazole, the most recently introduced atypical antipsychotic and a D2 receptor partial agonist, may also owe some of its atypical properties to its net effect of weak D2 antagonism, 5-HT2A antagonism and 5-HT1A agonism (30). By contrast, the alternative ‘fast-off’ hypothesis of Kapur and Seeman (31) applies only to clozapine and quetiapine and is inconsistent with the ‘slow off’ rate of most atypical antipsychotics, including olanzapine, risperidone and ziprasidone. 5-HT2A and 5-HT1A receptors located on glutamatergic pyramidal neurons in the cortex and hippocampus, 5-HT2A receptors on the cell bodies of dopaminergic neurons in the ventral tegmentum and substantia nigra and GABAergic interneurons in the cortex and hippocampus, as well as 5-HT1A receptors in the raphe nuclei are likely to be important sites of action of the atypical antipsychotics. Concurrently, a body of evidence has accumulated suggesting the important modulatory role of 5-HT2C and 5-HT6 receptors for some of the effects of a number of the current APDs. Thus, 5-HT has joined DA as a critical target for developing effective APDs and has led to the search for novel drugs with complex pharmacology, ending the exclusive search for single-receptor targets, e.g. the D3 or D4 receptor, and drugs that are selective for them. The important differences among these drugs are largely explained by their different affinities for the blockade of D2, cholinergic, histaminergic, 5-HT2A and 5-HT2C receptors. These neurochemical differences have important clinical implications both in terms of individual differences in treatment response and in common side effects. For example, olanzapine and quetiapine, which share the closest structural similarity to clozapine, are strongly antihistaminic and more sedating than the rest of the class (32). Olanzapine is probably second only to clozapine with respect to the incidence of associated metabolic complications (32, 33). Risperidone is the most potent D2 blocker within the class and, like haloperidol, binds tightly to DA receptors. As a result, at higher doses (>3 mg/day), risperidone therapy is associated with higher rates of EPS, hyperprolactinemia and galactorrhea than the other class members (34).

Ziprasidone and aripiprazole are the least sedating and probably have the lowest incidence of metabolic complications (33). Both medications are further distinguished within the atypical class by their relatively unique effects; whereas, ziprasidone and aripiprazole are potent antagonists of 5-HT1A receptors (32), only ziprasidone is a moderately potent inhibitor of norepinephrine and 5-HT uptake transporters (35). A partial agonist stimulates receptors when the target system is hypofunctional and antagonizes receptor activity when the targeted pathway is hyperfunctional. As mentioned earlier, aripiprazole is unique among the atypical antipsychotics in that it can also have agonist effects on D2 receptors under some circumstances (36). Because of the unique profiles of ziprasidone and aripiprazole, therapy may be complicated by excessive behavioural activation. It is worth noting that whereas the treatment-emergent behavioural activation observed during aripiprazole therapy is generally managed in the conventional way (i.e. by lowering the dose and slowing the rate of titration), the opposite strategy is more likely be helpful in ziprasidone therapy (37).

### Classes of Atypical Antipsychotic Drugs

The search for the mechanism of atypicality is complicated by the fact that the ‘prototype’ atypical antipsychotic, clozapine, shows effects at multiple receptors (i.e. dopamine D1, D2, histamine H1, serotonin 5-HT2, muscarinic M1) in addition to its effects on the dopamine D2 receptor (38). This in turn has led to several competing ideas about what...
makes clozapine atypical, with two principal conceptually contrasting themes. According to one theme, the actions of atypicals on non-D2 receptors are the key to atypicality, although accounts differ over which precise non-D2 receptor is critical. The actions at the serotonin 5-HT2 receptor (29, 38, 39), the serotonin 5-HT1A receptor as a partial agonist (40), the dopamine D1 (41), the dopamine D3 (42) and the dopamine D4 receptor (43, 44) have all been implicated. A contrasting theme (defended here) suggests that optimal modulation of the D2 receptor is a necessary and sufficient condition to obtain atypical antipsychotic activity (31, 43). Currently available atypical antipsychotic drugs include some that are relatively more potent 5-hydroxytryptamine (5-HT)2A antagonists than D2 antagonists \textit{in vivo}: clozapine, iloperidone, olanzapine, Org-5222 (asenapine), perospirone, quetiapine, risperidone, sertindole and ziprasidone. Aripiprazole is a partial dopamine D2 receptor agonist and has a higher affinity for this receptor than the 5-HT2A receptor (45), but does not produce extensive functional blockade of the D2 receptor \textit{in vivo}. These agents are sometimes referred to as multireceptor antagonists or, more irreverently, as ‘dirty drugs with rich pharmacology’ because they have high affinity for multiple receptors, which might have a bearing on their efficacy and side-effects (as discussed below). Remarkably, despite the plethora of such agents, none have been developed that are relatively selective for the 5-HT2A and D2 receptor. The closest to being selective might be blonanserin (46), which is still undergoing clinical testing but which appears to have atypical properties. The second class of atypical antipsychotic agent is the substituted benzamides, including amisulpride, remoxipride and sulpiride. These drugs are selective D2/D3 receptor antagonists, as are the typical neuroleptics, but differ in having very low affinity for any other type of receptor identified. It has been suggested that these agents are particularly useful in treating negative symptoms (i.e. withdrawal, flat effect, anhedonia, avolition and anergia), as well as depressive symptoms (47). In addition to these established agents, other types of drugs have been referred to as atypical antipsychotic agents on the basis of the definition of an atypical antipsychotic; that is, one which can treat the positive symptoms of schizophrenia while causing significantly lower EPS than the typical antipsychotics. Thus, selective D3 antagonists (48), D4 antagonists (49), M1 or M4 muscarinic agonists, NK3 antagonists and selective 5-HT2A or 5-HT2A/C antagonists have been proposed to be atypical antipsychotic agents; however, there is insufficient clinical evidence to be sure of their antipsychotic efficacy.

A key feature of atypical antipsychotic drugs, which distinguishes them from typical agents, is their preferential increase (in rodents) of DA release in the prefrontal cortex as opposed to the nucleus accumbens. The reverse is true for the typical neuroleptics drugs. This differential effect of atypical and typical antipsychotic drugs has been found to be largely caused by 5-HT2A antagonism, direct or indirect 5-HT1A agonism and weak D2 antagonism (50). Similarly, atypical agents increase acetylcholine (ACh) release in the prefrontal cortex of the rat (51); the basis for this increase is unclear but may be the result of dopamine D3 receptor blockade. These two effects might be important for the ability of atypical antipsychotic drugs to improve cognition in schizophrenia, as both DA and ACh have been shown to be involved in memory and learning. In addition to differential effects on DA, 5-HT and ACh, there are similarities and differences with regard to the effects of these classes of agents on the glutamate system, whose deficiency has been implicated in schizophrenia (48).

CLOzapine

Clozapine was first manufactured in 1959 and first marketed in the early 1960s (52), becoming widely used throughout Europe, because of its superior results in reducing psychotic symptoms with minimal EPS. Unfortunately, in 1975, 16 people in Finland developed severe blood reactions, a substantial decline in white blood cells (neutropenia), which made the individuals dangerously susceptible to infection (53). It was observed that clozapine could produce agranulocytosis at a much higher rate (1–2%) than that observed with standard antipsychotics. This led to clozapine’s withdrawal from the market (54) and only reintroduced, over a decade later, for sufferers of schizophrenia who were (a) resistant to typical neuroleptics and (b) compliant with blood monitoring. Treatment resistance is said to be present when the symptoms
of schizophrenia fail to respond to the usual drug treatment.

A strict blood monitoring system with regular white blood cell counts is mandatory in clozapine users. Blood cell counts must be performed weekly in the first 18 weeks of treatment and at least monthly thereafter. Approximately 50–80% of the cases of neutropenia or agranulocytosis occur in the first 18 weeks of treatment.

Its importance was once again duly recognized in 1988 when, in a 6-week double-blind comparison of treatment-resistant hospitalized patients, clozapine’s greater efficacy was demonstrated in 30% or more of the schizophrenic patients who had not responded to at least three attempts with other antipsychotics (55). Clozapine proved to be useful in the relief of positive as well as negative symptoms, and was well-tolerated in those patients who had not tolerated other antipsychotics. Based on these data, it was once again commercialized. However, its principal indication became, and continues to be, schizophrenia resistant to treatment with other antipsychotics.

The beginning of treatment with clozapine should, ordinarily, occur with patients free from other psychotropic drugs in order to minimize adverse events such as hypotension, sedation and anticolinergic effects and to avoid interfering with the benefits of clozapine that depend upon its weak blockade of D2 receptors (56). If necessary, however, an antipsychotic drug of high potency can be administered in low doses until the treatment with clozapine is established, in general within 2–3 weeks (57).

The initial recommended dose of clozapine is 12.5–25 mg, increasing gradually until doses of 300–450 mg/day are reached, generally within 2–3 weeks, taken at two intervals (half-life of 12–16 hours) (56). Elderly patients generally respond to 200–300 mg/day or to even lower doses. Notwithstanding, doses of up to 900 mg/day can be required. In Europe the clinical practice has been to administer doses of between 200 and 300 mg/day or less, whereas in the United States doses of 400–600 mg/day are more common (58).

Response to clozapine in patients resistant to treatment with classic antipsychotics may not be evident until after 6 months or even longer periods (18). Approximately, 30% of these patients respond in 6 weeks and another 30% respond more slowly (59), in up to 2 years (57).

Abrupt withdrawal of clozapine may be associated with the exacerbation of psychotic symptoms. When treatment is interrupted because of lack of compliance or for other reasons, and afterward re instituted, the response is generally similar; however, some cases of diminution in response have been reported. The reason for this is unknown (60).

When the total leucocyte count drops to 3000/mm$^3$ or neutrophil count to 1500/mm$^3$, clozapine should be withdrawn and blood counts with differential counting performed for 4 weeks. Clozapine can be reintroduced in patients interrupting treatment due to the presence of neutropenia, but more intensive monitoring is then indicated (18, 57).

Side-effects include hypersalivation, constipation, weight gain, orthostatic hypotension, tachycardia, high temperatures, convulsions and drowsiness. The incidence of EPS is practically nil and constitutes the main clinical advantage of treatment with clozapine, contributing significantly toward compliance (56). In comparison with typical neuroleptics, clozapine produces much less acatisia. There are no reports of confirmed TD. On the contrary, this can be treated with clozapine, where remission is observed in approximately 30% of cases and severity reduced in another 30%. Symptoms reoccur when clozapine is interrupted (18).

Excessive salivation occurs in around 30% of the patients. Reduction in the dose or treatment with anticolinergics can be beneficial. Clonidine, an alpha 2-adrenergic agonist, can also be useful for treatment of excessive salivation (61).

Clozapine does not elevate the serum levels of prolactin (PRL). Nevertheless, like all antipsychotics, it can cause neuroleptic malignant syndrome, albeit at a much lower rate (18). It is interesting to note that clozapine has been used successfully with patients who had developed this syndrome following the use of typical antipsychotics (57).

In conclusion, clozapine continues to be the prototypical atypical antipsychotic drug, although its use is limited to cases of treatment-resistant schizophrenia, patients with EPS and those suffering from TD.
RISPERIDONE

Risperidone is a benzisoxazolic derivative with a strong blocking effect on D2 receptors as well as 5-HT2 receptors. It connects with receptors α1, α2, and H1, also being a potent lysergic acid diethylamide (LSD) antagonist. However, it is practically devoid of anticolinergic effects. Risperidone is effective in treating the positive as well as negative symptoms of schizophrenia (62). Our group demonstrated, by means of a meta-analysis (63), that risperidone can be just as effective, or more effective and present less extrapyramidal effects, than haloperidol (10–20 mg/day), provided it is administered in doses of between 4 and 6 mg/day. Other data, also from meta-analysis (62), have demonstrated that risperidone is superior to haloperidol in its efficacy in treating negative symptoms. Risperidone’s efficacy involves a broad spectrum of symptoms of schizophrenia such as, positive and negative symptoms, disorganized thoughts, hostility and affective symptoms (64).

Risperidone produces fewer EPS than haloperidol when administered in doses lower than 8 mg/day. However, there are indications that this advantage is lost when using higher doses than this (19). Some other adverse effects common to risperidone are insomnia, agitation, sedation, dizziness, rhinitis, hypotension, weight gain and menstrual disturbances. Galactorrhea may be present, while there have also been reports of neuroleptic malignant syndrome (65).

Generally, the initial dose of risperidone is 1 mg twice daily, increasing up to 3 mg twice daily in the proceeding few days. Although, the optimum dose lies between 4 and 6 mg/day, larger doses could be necessary to control positive symptoms in some patients (18).

OLANZAPINE

Olanzapine, a tienobenzodiazepine, is an antipsychotic drug that possesses affinity for binding sites of dopamine D1–D4, serotonergics (5-HT2,3,6), muscarinics (sub-types 1–5), adrenergics (α1) and histaminergics (H1). Clinical trials have suggested that olanzapine diminishes the positive as well as the negative symptoms of schizophrenia and that it presents a low incidence of extra pyramidal effects (66).

Results of a meta-analysis carried out by our group (67) suggested that, at daily doses of 7.5–20 mg, olanzapine seems to be as effective, or more so, as an antipsychotic than haloperidol in the first 6 weeks of treatment. In doses of less than 7.5 mg/day however, haloperidol tended to be superior. Even greater safety was observed in the use of olanzapine as opposed to haloperidol, given that there was significantly less premature interruption of treatment because of the adverse effects with the former drug. Furthermore, patients treated with olanzapine needed much less anticolinergic medication, thereby suggesting that it produces significantly fewer EPS.

Overall, data from the four clinical trials with olanzapine presented a profile of light to moderate adverse effects, with the most common being sedation and weight gain. Anticholinergic effects and light dizziness were also observed. The effects concerning sexual dysfunction were minor (68).

In conclusion: (a) therapeutic failure was present in 48% of the patients treated with olanzapine as compared to 64% of those treated with haloperidol; (b) there were more premature interruptions in treatment for lack of efficacy among patients treated with haloperidol than among those treated with olanzapine; (c) premature interruption of treatment because of adverse effects was more frequent in patients treated with haloperidol than in those treated with olanzapine; and (d) the use of anticholinergics was necessary in only 15% of the patients treated with olanzapine, as compared with 49% of those treated with haloperidol (67).

Therefore, in the first 6 weeks of treatment with doses of 7.5–20 mg/day, olanzapine seems to be more effective, producing fewer EPS than haloperidol at doses of 5–20 mg/day (67).

QUETIAPINE

Quetiapine is a new antipsychotic that is structurally related to clozapine, but without the need for blood monitoring. Moreover, quetiapine possesses low to moderate affinity for the receptors 5-HT1A, 5-HT2, D1 and D2. The antagonism of these receptors, with predominant affinity for 5-HT2 in comparison with D2, is one of the key characteristics of its atypicality (69).

Randomized double-blind clinical trials indicate that the drug is as efficacious in the treatment of schizophrenia as reference antipsychotics, possessing low incidence of EPS and other side-effects (70–72).

The most frequently reported adverse effects are migraine headache (19%), sleepiness (19%) and dizziness (10%). The incidence of extrapiramidal symptoms is less than 10% (69).

Quetiapine proved to be as efficacious as chlorpromazine in treating the positive and negative symptoms, but with fewer collateral effects, including EPS. No hyperprolactinemia was observed in 101 patients treated with the drug, compared to the 100 control patients using chlorpromazine (73). The most efficacious doses are between 300 and 450 mg/day, although the usual range is from 150 to 750 mg/day. The doses should be increased gradually over several days (69).

ZIPRASIDONE
Ziprasidone, a benzotiazolilpiperazine, has more affinity for 5-HT$_{2A}$ than for the D$_2$ receptor. It is a potent agonist of 5HT$_{1A}$ and a potent antagonist of both 5HT$_{1D}$ and 5HT$_{2C}$ receptors. Ziprasidone has insignificant affinity for M$_1$ receptor and low affinity for alpha and H$_1$ receptors, which differentiate its profile from that of conventional antipsychotics and from other atypicals. These characteristics are responsible for the low probability of ziprasidone provoking EPS, postural hypotension, cognitive deficit and sedation (74).

In a double-blind clinical trial with a fixed dose and controlled by placebo (75), ziprasidone was significantly more efficacious than the placebo, improving the overall psychopathology of the patients with schizophrenia and schizo-affective disorders.

Ziprasidone can be used in the range of 40–160 mg/day divided into two daily doses. It is rapidly absorbed after oral administration where absorption is significantly increased by the presence of food in the organism. Ziprasidone is highly bound (>99%) to plasmatic proteins and is transformed into inactive metabolites by iso-enzyme 3A4 of cytochrome P450. Significant clinical differences were not demonstrated in relation to plasmatic concentrations and the half-life of elimination in different age groups. Therefore, there is usually no need to adjust dose according to age, gender or renal insufficiency. A small and transitory elevation of PRL could occur.

The most common adverse effects are headache, sleepiness, insomnia, nausea and constipation, in addition to dizziness, dyspepsia, diarrhea and asthenia. Ziprasidone provokes less EPS than conventional antipsychotics and has a very low incidence of weight gain.

Before prescribing ziprasidone, electrocardiographic evaluation should be considered because of its capacity to prolong QT interval. However, experience to date has not demonstrated any increased risk of clinical events attributed to QTc prolongation (76). It should not be associated with other medicines having this property, such as quinidine, thioridazine, sotalol, pimozide, moxifloxacin, etc.

The use of ziprasidone is contraindicated in patients who have recently suffered acute swelling of the myocardium, have arrhythmic cardiac insufficiency, a known history of prolongation of the QT interval or in those on class I or class III antidysrhythmic drugs.

ARIPIPRAZOLE
The atypical antipsychotic aripiprazole, with a mechanism of action that involves the notion of partial agonism of the dopaminergic receptors, is one of the newest antipsychotics launched worldwide (76, 77). In contrast to the dopaminergic antagonists, this partial agonist can act as an antagonist as well as agonist, depending on the functioning level of the dopaminergic circuit involved. This brings about a reduction in the dopaminergic neurotransmission when it is excessive (occurring in cases of psychosis with the hyperactive mesolimbic dopaminergic neurons that are responsible for positive psychotic symptoms) or an increase in the dopaminergic neurotransmission when it is very low (occurring when the mesocortical dopaminergic neurons responsible for negative and cognitive symptoms of schizophrenia are hypoactive/underactive). This property seems to be responsible for the lower incidence of extra pyramidal or endocrine side-effects, considering that aripiprazole appears to preserve the physiological action of the dopaminergic neurons that regulate motor activity and the liberation of PRL...
respectively. In addition, aripiprazole blocks the serotoninergic receptor 5-HT₂ (in a manner similar to the majority of the atypicals) (79) and the partial agonist 5-HT₁A (80).

Such characteristics make aripiprazole promising in the treatment of elderly patients with psychotic disorders (81, 82). However, more studies are needed to confirm this hypothesis.

CONCLUSION

The atypical antipsychotic drugs are a class of agents that have become the most widely used to treat a variety of psychoses because of their superiority with regard to EPS. The major concern regarding the safety of the atypical antipsychotics is related to their propensity to induce weight gain and alter glucose and lipid metabolism.

The majority of drugs that meet this definition of atypicality at the current time are relatively more potent as 5-HT₂A antagonists than D₂ antagonists. Even this class has other multiple pharmacological features that contribute to their efficacy and side-effect profile. Their main clinical advantage beyond low EPS is their ability to improve cognition (to some extent), which is one of the key deficits in schizophrenia. Further study is needed to define their mechanism of action, particularly with regard to long-term effects on neuronal plasticity and survival.

Conventional antipsychotics continue to be the first choice when just cost of treatment is considered, still a key factor in poor regions. It is likely that the next generation of treatments will have to move beyond reliance on a single drug as the sole treatment for the multidimensional disorder of schizophrenia. Optimal treatment of schizophrenia will probably require action on more than just the DA system. This does not mean that all the different targets need to be bundled in one pill. In fact, our current approach with multireceptor atypicals can be viewed as a kind of one-size-fits-all polypharmacy-in-a-pill. In most other branches of medicine, optimization of therapy for disorders involving more than a single physiological dysfunction (as is often the case in cancer, hypertension, arthritis) is usually achieved by different preparations each with its unique pharmacology and indications. Thus, we can envisage different therapeutic strategies in the future, each uniquely targeting a different dimension of schizophrenia, be it a positive, negative, cognitive or affective manifestation of the same syndrome. It will then be the physician’s job to flexibly target these signs and symptoms, and to titrate these strategies to match the dimensionality of the illness and its diverse manifestations in each patient.

REFERENCES


