ATYPICAL ANTIPSYCHOTICS: New Directions and New Challenges in the Treatment of Schizophrenia

Shitij Kapur1,2,3 and Gary Remington1,3
1Schizophrenia Program, 2PET Centre, CAMH, Toronto, 3Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario, Canada M5T 1R8; e-mail: skapur@camhpet.on.ca

Key Words clozapine, dopamine, serotonin, psychosis

Abstract “Atypical” antipsychotics represent a new generation of antipsychotics with a significantly lower incidence of extrapyramidal side effects (EPS), as well as little or no effect on prolactin elevation. These advantages constitute a major improvement in the treatment of patients with schizophrenia. The exact mechanisms that make these drugs atypical is not clear. However, a preferential action on serotonin 5-HT2 or D4 receptors, or a more rapid dissociation from the dopamine D2 receptor, may account for atypicality. Although the atypical antipsychotics have overcome EPS, other side effects such as weight gain and impaired glucose tolerance/lipid abnormalities have come to the fore. Thus, the challenges are far from over. The current atypicals are much more effective against the psychosis of schizophrenia than against the other, more enduring aspects of this disorder, e.g. negative symptoms and cognitive dysfunction. At present, the atypicals use a “pharmacological shotgun” strategy to treat aspects of the disease in all patients. A more sophisticated and perhaps effective approach to schizophrenia may lie in independently targeting the pathophysiological mechanisms of each clinical dimension (i.e. positive, negative, cognitive, and affective) with more selective drugs that can be combined and individually titrated to the needs of each patient.

INTRODUCTION

It is ironic that the drugs most commonly used to treat schizophrenia are called “atypical.” But this nomenclature is not accidental—we know more about how these newer antipsychotics differ from the older typical antipsychotics than we know about what truly unites them. This review introduces the concept of atypical antipsychotics, points out what is new about them, and reviews what challenges lie ahead in the treatment of schizophrenia.
Definition of Atypical Antipsychotics

The use of the term atypical to describe an antipsychotic drug can be traced to the drug clozapine (1). Clozapine seemed atypical in that it did not cause extrapyramidal side effects (EPS) in patients or catalepsy in animals, in contrast to the prevailing antipsychotics (haloperidol and chlorpromazine). Through the 1970s and 1980s, “atypical” was synonymous with clozapine. However, with its clinical introduction, additional unique features were highlighted. Specifically, clozapine was found to (a) be effective in at least some patients for whom the typical neuroleptics had failed; (b) show preferential effects on the so-called negative symptoms (apathy, amotivation, etc); and (c) demonstrate possible benefits on symptoms related to mood and cognition (2). As a result of these findings, the term atypical is used in such varied contexts that it is losing much scientific value.

Although experts can barely agree on a formal definition of atypicality, there is nearly unanimous agreement that all the newly introduced antipsychotic drugs are atypical. This list includes risperidone, olanzapine, and quetiapine in North America; ziprasidone is the next likely entry. In other parts of the world, amisulpiride, sertindole, and zotepine have gained atypical status.

A recent meta-analysis of these atypical antipsychotics suggests that their greatest similarities lie in their diminished risk of EPS and lack of prolactin elevation. The effect size differences in this regard are large (in the range of 0.3 or greater) (3, 4). Beyond these two criteria, though, the similarities are modest and inconsistent. For example, as a class, these drugs have not shown superiority to typical antipsychotics in improving negative symptoms. There has been a suggestion of superiority on this dimension with some of the atypicals (olanzapine and risperidone), but the effect size is very small (<0.1), and one cannot be sure that it is not secondary to the lack of EPS (3). Although changes in other symptoms such as cognition have been reported for some of these drugs, the effect size once again is limited and variable (5). In summary then, the word atypical should mean an antipsychotic with low EPS and lack of sustained prolactin elevation. Effects on a number of other features of schizophrenia, such as negative symptoms, mood, cognition, and functional outcome, are all very desirable clinical therapeutic goals. However, they are neither consistently realized nor of substantial magnitude with the current generation of antipsychotics.

What is the Psychopharmacological Basis of an Atypical Antipsychotic?

All antipsychotics, typical as well as atypical, have relevant affinities for the dopamine D2 receptor (6, 7). In fact, the in vitro affinity of a drug at the dopamine D2 receptor still remains the single best predictor of its dose in a clinical situation (8, 9). What distinguishes the atypical antipsychotics from their typical counterparts is not clear, and there may well be more than a single mechanism for achieving atypicality. Several current competing theories are reviewed below.
**High Affinity for 5-HT$_2$ Receptors**

It has been proposed that a high affinity for 5-HT$_2$ receptors, particularly a higher affinity for 5-HT$_2$ versus D$_2$ receptors, may be the key to atypicality (10–12). Data from animal studies and basic neurobiology do provide evidence that manipulation of the 5-HT$_{2A}$ system may modulate the effects of the D$_2$ system (13, 14). Although this is the most prevalent hypothesis currently, there are several hurdles. First, there has been no direct demonstration that the addition of 5-HT$_2$ antagonism to ongoing treatment through D$_2$ blockade leads to an atypical profile of antipsychotic effects. Second, several typical antipsychotics actually have very high affinity at the 5-HT$_2$ receptor. Conversely, many of the atypical antipsychotics seem to lose their atypical characteristics when used in high doses, which suggests that high affinity for 5-HT$_2$ may not be a sufficient explanation for atypicality (15, 16). Third, drugs that have a very high affinity for the 5-HT$_2$ receptor alone, without any notable affinity for the D$_2$ receptor (e.g. ritanserin and MDL 100,907), have failed to show a reliable antipsychotic effect, typical or atypical. Finally, one of the atypical antipsychotics commonly used in Europe, amisulpride, is a relatively pure dopamine D$_2/3$ antagonist, devoid of notable 5-HT$_2$ properties (17). Thus, although most of the current atypical antipsychotics do have a higher affinity for 5-HT$_2$ receptors than for D$_2$ receptors, the sum of evidence suggests that the affinity is neither necessary nor sufficient for atypicality.

**High Affinity for Dopamine D$_4$ Receptors**

The role of dopamine D$_4$ receptors was suggested by the finding that clozapine, the prototypical atypical antipsychotic, shows a very high affinity for this particular receptor relative to its affinity for the D$_2$ receptor (18). This idea gained further support through preliminary evidence that patients with schizophrenia may have a several-fold elevation of D$_4$ receptors (19). However, several lines of evidence seem to contradict this proposal. First, the elevation in D$_4$ receptors claimed originally has not been reliably replicated (20). Second, other antipsychotics, including typical agents, also have a high affinity for the D$_4$ receptor (e.g. haloperidol’s affinity for the D$_4$ receptor is higher than clozapine’s). Finally, experimental drugs with a selective affinity for the D$_4$ receptor have been shown to be devoid of antipsychotic activity in clinical trials (21).

**Fast Dissociation from Dopamine D$_2$ Receptors**

A more recent suggestion is that the basis of atypical antipsychotics may lie in their rapid dissociation from the dopamine D$_2$ receptor (7, 22). This proposal is buttressed by a recent finding that affinity of the antipsychotics for the D$_2$ receptor is highly correlated with their rate of dissociation. Drugs with low affinity for the dopamine D$_2$ receptor dissociate from the receptor much more quickly, and this low affinity/fast dissociation at the D$_2$ receptor is the single best predictor of atypicality. However, the mechanisms by which rapid dissociation leads to atypicality are yet to be elucidated. It has been suggested that rapid dissociation allows the drug to be more responsive to endogenous dopamine, thereby permitting antipsychotic activity but avoiding side
effects related to dopamine blockade, such as EPS and hyperprolactinemia. This hypothesis can account for the major features of atypicality and can explain the above-noted discrepancies of the 5-HT₂ and D₄ hypotheses, while explaining why a drug such as amisulpride, a relatively pure D₂ antagonist, would be atypical.

THE ATYPICAL ANTIPSYCHOTICS

Clozapine, the prototype of atypical antipsychotics (1), was introduced for clinical use in a small number of countries in the early 1970s. However, shortly after introduction there were fatalities reported, subsequently attributed to a risk, albeit low (<1%), for clozapine to cause agranulocytosis. This led to a severe curtailment in its use, and it was not until the 1980s that the drug was reintroduced in North America, this time with the requirement of mandatory blood monitoring on a regular basis. Because of this history, clozapine use has been restricted to those individuals who have failed to respond to alternative antipsychotics.

An important contribution of clozapine was its ability to dissociate antipsychotic action from EPS action—a feature that encouraged researchers to exploit this dissociation in other drugs (3, 6, 23–25). In North America, the reintroduction of clozapine was followed by other antipsychotics that fit the atypical profile: risperidone, olanzapine, and more recently, quetiapine. Sertindole was submitted to the US Food and Drug Administration (FDA) for approval but was subsequently withdrawn owing to cardiac conduction issues, specifically prolongation of the QTc interval. Ziprasidone is another atypical antipsychotic that has undergone extensive phase III testing and has recently been approved by the FDA, with some extended testing to assure its safety with regard to QTc prolongation. In parts of Europe and Asia, two other atypical antipsychotics have been approved for use, amisulpride and zotepine (25). Table 1 highlights features of these approved atypical compounds.

CLINICAL OUTCOME MEASURES

Historically, the focus of pharmacotherapy in schizophrenia has been treatment of psychosis. More recently, driven largely by the investigation of newer antipsychotics, other symptom clusters (negative, cognitive, and affective) have been identified, and schizophrenia and its symptoms are now viewed along a number of dimensions (26–28). Although each of the four symptom clusters is reviewed separately below, it is essential to recognize that clinically they are interrelated. Thus, improvement in one type of symptom may be associated with benefits in other symptoms as well; the reverse may also hold true when certain symptoms worsen. It is also important to recognize that at least three distinct populations of patients with schizophrenia exist: (a) those in their first episode or early in the course of treatment, a group that generally appears more responsive to treatment;
TABLE 1  Pharmacological and selected side-effect profile of atypical antipsychotics (activity at D2 receptors is still the only property that unites atypical agents)

<table>
<thead>
<tr>
<th>Agents</th>
<th>Haloperidol</th>
<th>Amisulpride(^a)</th>
<th>Zotepine(^a)</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Sertindole(^b)</th>
<th>Ziprasidone(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Class</td>
<td>Butyrophenone</td>
<td>Benzamide</td>
<td>Dibenzo-thiepine</td>
<td>Dibenzo-diazipine</td>
<td>Benz-isoxazole</td>
<td>Dibenzo-oxepine</td>
<td>Dibenzo-thiazepine</td>
<td>Indole</td>
<td>Benzo[thiazo]-piperazine</td>
</tr>
<tr>
<td>Receptor Binding Profile (^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>𝑃 1</td>
<td>+++</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>𝑃 2</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++ +</td>
</tr>
<tr>
<td>5-HT(_2)</td>
<td>+</td>
<td>–</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>𝑋 1</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>𝑋 2</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>𝐻 1</td>
<td>–</td>
<td>–</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>𝐻 2</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Side Effect (^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPS</td>
<td>++++</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>–</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Prolactin</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++++</td>
<td>++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Abnormal GTT(^e)</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Lipid increase(^e)</td>
<td>–</td>
<td>?</td>
<td>?</td>
<td>+++</td>
<td>?</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

\(^{a}\)Not available in North America.
\(^{b}\)Withdrawn.
\(^{c}\)Pending regulatory approval in North America.
\(^{d}\)D = dopamine; 5-HT = serotonin; a = adrenergic; H = histamine; M = acetylcholine (muscarinic).
\(^{e}\)Limited published data available.
(b) a large group (in fact the majority) who show complete or partial remission but need maintenance medications for a lifetime; and (c) a smaller subgroup of patients who prove truly refractory to various antipsychotics (29, 30).

Positive Symptoms

Treatment of psychosis (e.g. delusions and hallucinations) is a definitional requirement for an antipsychotic, and all atypical antipsychotics are more effective than placebo. Beyond this basic requirement, one should ask: Are the atypical antipsychotics superior to typical antipsychotics, and is there a preferential efficacy of these drugs in patients who have failed to respond to the older, typical antipsychotics?

The appropriate design to answer these questions would be to randomize a series of antipsychotic-naive patients to receive either typical or atypical treatments. Definitive studies are lacking, and the few studies that have included at least a subgroup of drug-naive individuals show equivocal results (31, 32). Most of the systematic data pertain to patients who had partial response to typical antipsychotics and were then randomized to receive either a typical antipsychotic or a new atypical antipsychotic. The very design of such studies introduces a selection bias in favor of the newer atypical antipsychotics. However, even these trials show only marginal evidence that the atypical antipsychotics may be superior (3).

In the refractory population, clozapine has been extensively tested, partly because it is largely limited to use in this population. Several, but not all, studies have found it superior to typical antipsychotics. Data on the other atypical antipsychotics are relatively limited, but there is some suggestion of preferential benefit in these refractory patients (29).

Negative Symptoms

Negative symptoms reflect a more insidious aspect of schizophrenia, which often precedes the onset of positive symptoms. Negative symptoms include apathy, lack of motivation, and lack of interpersonal and social drive/interaction (33–35). It is heuristically useful, though practically very difficult, to distinguish primary negative symptoms (also referred to as deficit symptoms) from secondary negative symptoms. Primary negative symptoms are thought to reflect an inherent component of the illness, whereas secondary negative symptoms result from other factors, e.g. poorly controlled positive symptoms, antipsychotic-induced EPS, and institutionalization (36). Contrary to common thinking, typical antipsychotics are definitely effective in the treatment of negative symptoms, although the degree of effect on these symptoms is usually less than that on positive symptoms (37). However, typical antipsychotics are more prone to cause secondary negative symptoms in the form of EPS.

Do atypical antipsychotics have a greater effect on negative symptoms than typical antipsychotics do? The data are mixed (3, 29). Large meta-analyses suggest that the recommended therapeutic doses for risperidone and olanzapine,
compared with a 10–20 mg/day dose of haloperidol (which exceeds current dosing guidelines), confers a 7% greater improvement in negative symptoms. However, all the current trials suffer from a major confound: The high doses of typical antipsychotics used in these trials are much higher than optimal and are likely to be associated with medication-induced secondary negative symptoms. Thus, it remains an open question whether the slight superiority documented for the atypicals simply reflects their propensity to give rise to lesser EPS or whether there is an independent improvement in primary negative symptoms.

Affective Symptoms

Depressed mood is a common feature in schizophrenia. As with negative symptoms, diagnosis can be difficult (38). For example, affective and negative symptoms can often look similar; moreover, it is not always easy to distinguish clinical depression from the chronic dysphoria that can characterize a severe and debilitating illness such as schizophrenia. Affective symptoms also characterize the prodrome (39), and it is not uncommon for a diagnosis of depression to be made first, only to be revised as the psychosis emerges.

There is some encouraging evidence that the newer atypical antipsychotics may have a preferential effect on mood symptoms in schizophrenia (25, 29, 40, 41). Given that atypicals have a major effect on the serotonergic system, this is a plausible outcome. However, these data are drawn mainly from trials in which affective symptom change was not a primary outcome measure, and scales specific to depression were lacking. In addition, as with negative symptoms, the adverse influence of typical antipsychotics in high doses cannot be ruled out. Finally, it is unclear whether the identified superiority of atypical antipsychotics in treating affective symptoms is comparable to that obtained through the addition of an antidepressant.

Cognitive Symptoms

Cognitive abnormalities have been demonstrated in individuals having their first episode of psychosis, and there is a suggestion that cognitive abnormalities, more than psychotic symptoms, predict long-term functional (versus clinical) outcome in schizophrenia (42–45). The effects of both the typical and atypical antipsychotics on remediation of cognitive function are unclear (46). There is a general consensus that typical antipsychotics offer no appreciable improvement in cognitive symptoms, and may even be detrimental because of their EPS. The atypical antipsychotics have been held out as promising in this area, although for a number of these agents, the data are just emerging. Although the issue of cognition has taken on increased importance in schizophrenia research, the variety of measures used in different studies, the lack of consistency between reported benefits, and the uncertain extrapolation of these findings to real-world functioning remain significant problems.
Other Domains

In the development of these newer antipsychotics, there has been a much more detailed and comprehensive evaluation of their potential benefits. Outcome measures have extended to more global issues such as quality of life (41, 47). Again, the results to date have favored the atypical agents, although the degree of difference from their conventional counterparts has not been overwhelming. Other unusual findings have been reported. For example, clozapine has been associated with a decreased rate of suicide (48), a clinically significant finding given that approximately 10% of those with schizophrenia will kill themselves. Clozapine has also been linked with decreased substance abuse (49), another problem that has a much higher prevalence in schizophrenia than in the general population. However, it is too early to know whether these findings will prove reliable, or whether they can be generalized to all atypical compounds.

SIDE EFFECTS

Efforts to develop newer antipsychotics have been driven by two goals: improved efficacy and a more benign side effect profile. Since their introduction into clinical use, antipsychotics have been associated with a number of troublesome side effects that have, in turn, been linked to compliance problems (6, 25, 50–52). The first agents available, e.g. chlorpromazine, were discovered serendipitously. Since they acted on several aminergic and cholinergic receptors, they commonly gave rise to a variety of side effects such as dry mouth, urinary and bowel motility disturbances, sedation, and cardiovascular complications. With the recognition that they seemed to effect their antipsychotic response through D2 blockade, efforts shifted to the development of selective D2 antagonists, e.g. haloperidol, and these antipsychotics were identified as high-potency conventional antipsychotics. Unfortunately, this increased potency at the D2 receptor came at the cost of an increased risk of EPS, the side effects that came to characterize this class of typical antipsychotics. Paradoxically, the atypical antipsychotics have returned us to a class of compounds that are more heterogeneous in their receptor profile. As a result, although we have made significant gains in relegating EPS and prolactin side effects to the background, new side effects, related to the promiscuous receptor profile of the atypicals, are now emerging.

A review of all side effects is beyond the scope of this chapter. The focus here is confined to those side effects linked to D2 blockade (EPS and hyperprolactinemia), as well as weight gain and impaired glucose tolerance, which have been identified as the most problematic adverse effects with the current group of atypical antipsychotics.

Extrapyramidal Side Effects

Antipsychotic-induced EPS have been associated with the drugs’ D2 blockade at the level of the nigrostriatal pathway. A major advantage of atypical antipsychotics
is their relative freedom from this group of side effects (6, 24, 25, 29, 53, 54). Once again, though, it must be pointed out that the comparative doses for the conventional antipsychotics in many of the initial clinical trials were inappropriately high. In addition, atypical antipsychotics are not equal along this dimension. Risperidone’s risk is dose-related, as is olanzapine’s, although the latter seems to carry a comparatively lower risk of overt EPS, perhaps related to its inherent antimuscarinic activity (16, 55–57). Clozapine and quetiapine carry a very low risk of EPS. This has been attributed to their very fast dissociation from the D₂ receptor, which results in lower D₂ occupancy across time (7, 22, 58).

Tardive dyskinesia (TD) occurs in approximately 25% of individuals exposed to ongoing use of typical antipsychotics, a figure that is even higher in certain subgroups, e.g. the geriatric population. With their decreased risk of acute EPS, it has been postulated that the atypical antipsychotics may carry a diminished risk of TD, since sustained EPS have been identified as a risk factor for TD (59). A diminished risk of TD has been established for clozapine (60), the atypical that has been available longest, and the early data for other atypicals seem promising in this respect (61, 62). At least some of the newer antipsychotics have been shown to have anti-dyskinetic properties in individuals who have existing TD owing to previous antipsychotic exposure (63–65).

Hyperprolactinemia

All typical antipsychotics have been linked to a risk of elevated prolactin, associated with D₂ blockade of the tuberoinfundibular pathway. As a class, the atypical drugs are free of sustained prolactin elevation, although one of them, risperidone, still has a relatively high incidence of this side effect (66–68). The precise reason for this is not clear; however, a higher peripheral level of risperidone plus 9-hydroxyrisperidone in the plasma (as related to the brain) may be responsible, since the prolactin-elevating effects of antipsychotics are exerted outside the blood-brain barrier, whereas their antipsychotic efficacy arises from their central effects. The more immediate consequences of hyperprolactinemia, e.g. galactorrhea and amenorrhea, cannot be overlooked in the clinical setting. In addition, there is growing concern regarding potential long-term consequences; although not well understood, these may include osteoporosis, altered immune function, and risk for certain types of cancer (4).

Weight Gain and Impaired Glucose Tolerance

Weight gain has always been an issue with antipsychotics, but as a side effect it has historically been overshadowed by the risk of EPS. Atypical antipsychotics, as a class, carry a much lower risk of EPS but a much greater risk of weight gain. Olanzapine and clozapine seem particularly problematic in this respect (69, 70). It has been suggested that ziprasidone may be largely free of this side effect (71, 72), but this drug has not seen widespread clinical use. The mechanisms underlying
this drug-induced weight gain are not entirely clear; both the serotonin 5-HT$_{2C}$ and the histamine H$_1$-blocking activity of these drugs have been implicated (69).

The degree of weight gain can be substantial, e.g. as much as 30 pounds or more, a problem made more serious by other features of the population who must receive ongoing antipsychotic therapy. Patients with schizophrenia tend to have poor levels of nutrition, a 70% prevalence of smoking, and little or no preventative health care, so the cardiovascular risks associated with weight gain take on even greater importance.

Another issue coming to the fore is the potential impact of atypical antipsychotics on glucose tolerance. A growing number of reports indicate new-onset diabetes in individuals being treated with atypical antipsychotics, and evidence gathered to date has indicated that risk of diabetes mellitus and/or impaired glucose tolerance may be at least twice as common in individuals on atypicals than in patients on typical agents (73, 74). Again, drugs such as clozapine and olanzapine seem to be the worst offenders. In fact, a recent study suggests that the overall incidence of diabetes in patients taking clozapine may rise to an astronomical 37% in 5 years of follow up—a consequence at least as troubling as the TD problems associated with the typical antipsychotics (75). Early data suggest that risperidone may be less problematic along these dimensions; data on quetiapine and ziprasidone are lacking.

Yet another related problem is increased levels of lipids, specifically triglycerides (76, 77). The underlying mechanisms are not clear, but the overall impairment of glucose tolerance seems to be consistent with insulin resistance. These changes could simply be secondary to weight gain, but the precise relationship is not clear, and there is the possibility that these glucose/lipid abnormalities are independent. The second possibility is particularly worrisome because weight gain, glucose intolerance, and lipid abnormalities are all independent risk factors for cardiovascular mortality. Regardless of etiology, regular weight monitoring and glucose/lipid profile assessments are now advocated for patients receiving atypical antipsychotics.

ANTIPSYCHOTICS: Looking into the Future

The new generation of antipsychotics represents a step forward in the treatment of schizophrenia. There is a definite improvement in tolerability and some evidence of improved efficacy. However, the challenges are far from over. A significant proportion of patients still do not experience complete remission of their positive symptoms. Primary negative and cognitive symptoms remain largely unchanged, and functional recovery, though improved, is still poor. Moreover, these newer antipsychotics have brought with them their own profile of side effects: weight gain, diabetes, and lipid abnormalities. Better drugs for treating schizophrenia are needed as much today as 10 years ago.
Current atypical antipsychotic treatment of schizophrenia represents a shotgun approach, in contrast to the rest of medicine, where drug development has led to more precise and specifically targeted medications. A more precise model of the different dimensions of schizophrenia should guide the next generation of targeted drugs. One such heuristic model is provided in Figure 1.

The etiology of schizophrenia includes genetic as well as environmental causes, the precise nature of which is unknown. Long before the psychosis presents, cognitive, primary negative (deficit), and affective symptoms appear and have a subtle but detrimental effect on the individual’s level of functioning and interpersonal relationships. Against a background of genetic and environmental vulnerability, and in the presence of subtle negative/cognitive abnormalities, arises psychosis, a sine qua non for the diagnosis of schizophrenia. As the model illustrates, this axis of psychosis, behavioral disruption, and secondary negative symptoms stands largely on the pillar of dopaminergic dysregulation. Although the basis for the negative and cognitive symptoms is still unclear, it is unlikely to be the same as that of the positive symptoms.

As illustrated in Figure 1, the dopamine/psychosis axis and its secondary consequences respond most readily to the current atypical antipsychotics, which remain mainly antidopaminergic drugs. However, the ability to treat other features, i.e., primary negative symptoms, psychophysiological and interpersonal deficits, and cognitive and affective symptoms, is limited. In addition, although the current drugs can control the expression of hyperdopaminergia (as demonstrated in Figure 1), they do not remit the underlying causes of dopamine dysregulation. As a result, psychosis and related dopaminergic abnormalities return rather readily when these medications are stopped.
Although it is widely agreed that schizophrenia is a heterogenous disorder with multiple dimensions, we still treat it with a single drug that includes a cocktail of receptor blockades. A more sophisticated pharmacological approach would be to define the different dimensions, develop targeted treatments for each, and combine these drugs in a flexible manner to address a patient’s individual requirements along the different dimensions. Until such a time is reached, we hope that the intelligent use of atypical antipsychotics, with particular attention to weight gain and impaired glucose tolerance, combined with active and focused psychosocial rehabilitation, shall be our ally.

**Visit the Annual Reviews home page at www.AnnualReviews.org**

**LITERATURE CITED**


A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. Arch. Gen. Psychiatry 57(6):553–59