Dopamine D_2 Receptors and Their Role in Atypical Antipsychotic Action: Still Necessary and May Even Be Sufficient

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"Atypical" antipsychotics are associated with a much lower propensity for extrapyramidal side effects and, with some exceptions, a lack of sustained prolactin elevation. The authors propose that a low-affinity and fast dissociation (in molecular terms) from the dopamine D_2 receptor, along with administration of the drug in doses that lead to appropriate levels of dopamine D_2 receptor blockade, are the most important requirements for atypicality. Actions at other receptors (5-HT_2, D_4, etc.) may not be necessary to achieve atypicality, and while action at these receptors may have benefits on symptoms such as mood and cognition, this is as yet to be conclusively proven. Why clozapine is effective in refractory patients is still elusive and efforts to make antipsychotics that are devoid of effects on the dopamine D_2 receptors so far have been unsuccessful. In light of this, the authors provide a heuristic model linking pathophysiology and therapeutics and suggest that the ideal treatment for schizophrenia is unlikely to be single-drug with multireceptor blockade (a sort of one-size-fits-all polypharmacy) but will require several specific and targeted treatment strategies that are titrated to match the variable expression of different dimensions of schizophrenia in each patient. Biol Psychiatry 2001;50: 873–883 © *2001 Society of Biological Psychiatry*

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Introduction

It is an interesting irony that in the treatment of schizophrenia, the most commonly used medications are called "atypical." This terminology probably reflects that fact that we know much more about what differentiates these drugs from the "typical" antipsychotics, rather than what unites this class of drugs. This article is not presented as a comprehensive synthesis of all views regarding atypicals but expands on one competing idea of what makes antipsychotics "atypical" (Kapur and Remington 2001; Kapur and Seeman 2001). Competing perspectives on this issue are defended elsewhere (Meltzer 1999), and the reader is referred to more comprehensive reviews (Arnt and Skarsfeldt 1998; Arnt et al 1997). Although we do not review all perspectives in detail, we do point out how our ideas differ from them. Furthermore, it is not the intent of this article to examine the differences between atypicals, although there may be significant differences between drugs within the class of "atypical."

The article is presented in four sections. In the first section, we review the clinical feature that most reliably distinguishes the atypical antipsychotics from typical antipsychotics. In the second section, we examine the molecular pharmacologic features of these drugs in preclinical models and the different hypotheses that have been forwarded to explain atypicality. In the context of these findings, we review the receptor imaging studies of typical and atypical antipsychotics. Finally, we provide a heuristic model that tries to unite current understanding regarding the pathophysiology of schizophrenia to the mechanism of action of atypical antipsychotics.

Atypical Antipsychotics—Distinguishing Clinical Features

The current use of the term *atypical antipsychotics* can be traced to the earliest preclinical studies with clozapine, in which it was distinguished from the other typical antipsychotics of that era by not inducing catalepsy in animal models or extrapyramidal side effects (EPS) in patients (Hippius 1989). As clinical trials with clozapine mounted, other unique clinical features were proposed, including efficacy in patients refractory to "typical" antipsychotics (Kane et al 1988) and increased effectiveness in negative, affective, and cognitive symptoms, as well as in various functional and psychosocial domains (Wahlbeck et al 2000). Thus, the standard was set by which newer antipsychotics were to be measured. There are now two

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systematic meta-analyses that have combined trials examining more then 12,000 patients on an atypical drug versus an active comparator, placebo, or both (Geddes et al 2000; Leucht et al 1999). Unequivocal evidence exists that atypical antipsychotics have fewer EPS, require less anticholinergic use, and have a superior tolerability profile. This holds true even in trials with modest doses of haloperidol as a comparator (Zimbroff et al 1997) and when high doses of the comparator are controlled for statistically (Geddes et al 2000). Furthermore, there is considerable evidence that most of the newer atypical antipsychotics (with the interesting exception of risperidone, which elevates prolactin, probably because of blood–brain barrier anomalies; Bowden et al 1992) have a lower incidence of prolactin elevation than the older typical antipsychotics (Peuskens 1997).

The data on superior efficacy against positive symptoms are conflicting. Whereas one study found no class advantage (Leucht et al 1999), another found an advantage in efficacy (Geddes et al 2000); however, doses for the comparator antipsychotics have often been excessive, and controlling for this factor eliminated such an advantage. Some of the atypicals (olanzapine, risperidone) do show an advantage in efficacy against positive symptoms but only when studies include hundreds of patients, suggesting that the effect size is rather small (Leucht et al 1999). The advantage is further compromised by a bias inherent to virtually all these studies, that is, the recruitment of patients already known to respond only partially to typical antipsychotics. There are few prospective controlled studies in first-episode patients, and the only one publicly available fails to show enhanced efficacy against positive symptoms (Emsley 1999). A recent study of haloperidol versus olanzapine in first-episode patients has been completed, although the results are not yet public. A further bias characterizing these studies is that the newer drugs are on average much better tolerated and show a lower drop out rate. When data from these studies is compared using a last-observation-carried-forward model, it sometimes can convert a tolerability advantage into an apparent efficacy advantage.

The other area of great interest is that of negative symptoms. Typical antipsychotics are effective in the treatment of negative symptoms (Leucht et al 1999); the question is whether atypicals are superior in this respect. Current evidence, in fact, indicates no class advantage of atypical antipsychotics in negative symptoms (Leucht et al 1999). Although some antipsychotics (risperidone and olanzapine) do show a modest advantage (Leucht et al 1999), it is unclear whether this represents a primary effect or instead reflects a lack of EPS and the related motor and dysphoric effects. Indeed, this issue is still unclear with respect to the prototype atypical, clozapine (Buchanan et al 1998; Essock et al 1996; Rosenheck et al 1999).

Similarly, there is increasing interest that the atypical antipsychotics may have an additional efficacy on mood and cognitive symptoms. Most of the data, however, pertain to post hoc and subscale analysis of studies that were not designed to investigate this issue. At best, the present data can be seen only as suggestive, and it is possible here as well that the identified superiority could simply reflect the diminished risk of Parkinsonism, in this case the so-called "cognitive Parkinsonism" that has been associated with typical antipsychotic use. In conclusion, the single feature that unites atypical antipsychotics and clearly distinguishes them from their typical counterparts is diminished EPS and (with some exception) prolactin elevation. In terms of superior efficacy on positive and negative symptoms, there is modest improvement with the newer atypicals, but at this time it is unclear whether this improvement can be sustained beyond the confounds of selection bias and dose inequities. It should also be pointed out that even though two drugs may have roughly equal "efficacy" in controlled clinical trials, they may have very different "effectiveness" in the real world. Because atypical antipsychotics give rise to fewer EPS and are generally better tolerated, they may lead to higher compliance and therefore to greater effectiveness.

Atypical Antipsychotics: What Is Atypical about Their Molecular Pharmacology?

Given that all antipsychotics, typical as well as atypical, block dopamine D_2 receptors (Creese et al 1976; Kapur and Seeman 2001; Seeman et al 1975; Seeman and Lee 1975), it is reasonable to expect that differences between typical and atypical antipsychotics arise from some non-D_2-receptor activity. Various candidates have been proposed: 5-HT_2 (Meltzer et al 1989a), D_4 (Van Tol et al 1991), glutamate (Olney and Farber 1994, 1995), alpha adrenergic receptors (Svensson et al 1995), and others (Gerlach and Casey 1994). Of these, the serotonin 5 HT_2 and the dopamine D_4 system have received particular attention.

The Serotonin–Dopamine Hypothesis

The serotonin–dopamine hypothesis proposes that the unique feature of an atypical antipsychotic is its greater affinity to bind to the serotonin 5-HT_2 than the dopamine D_2 receptors. This hypothesis was first articulated by Meltzer and colleagues, who noted that the atypical antipsychotics had nearly 10 times greater affinity for the 5-HT_2 than dopamine D_2 receptors, in vitro as well as in vivo (Meltzer et al 1989a; Meltzer et al 1989b; Stockmeier

et al 1993). Overlooked in subsequent discussions, however, has been the important point that the difference between typicals and atypicals was not in their affinity for the serotonin 5-HT_2 receptor, but in their dopamine D_2 receptor. For the total 20 typicals and 17 atypicals (Meltzer 1989a), the mean affinity at the 5-HT_2 receptors (expressed as pKi) was 8.37 for typicals and 8.36 for atypicals, with no statistical difference between them. In contrast, the D_2 affinity of the typicals was 8.88 and 7.02 for the atypicals, the difference being highly significant. In fact, Meltzer and colleagues reported a discriminant function analysis of the data clearly showing that the difference between atypicals and typicals was not their 5-HT_2 but their lower D_2 affinity (the relative variance explained was 17% and 64%, respectively). Although all the current atypicals in North America conform to this high 5-HT_2 and low D_2 rule, several lines of evidence raise questions whether the 5-HT_2 is causally necessary for atypicality. First, it is now clear that several of the typical antipsychotics (loxapine, chlorpromazine) have a high affinity for the serotonin 5 HT_2 receptors in vitro and show almost complete saturation of these receptors at clinical doses (Kapur et al 1997; Trichard et al 1998). Second, drugs with selective 5-HT_2 blocking properties such as MDL-100907 (Announcement 1999) and fanaserin (Truffinet et al 1999) have not shown conventional levels of antipsychotic efficacy. In fact, MDL-100907 was found not to be superior to placebo in patients with only negative symptoms (Announcement 1999). Finally, remoxipride (Lewander 1994; Lewander et al 1992) and amisulpride (the former was withdrawn due to aplastic anemia and the latter is used extensively in France) show features of atypicality without affinity for the serotonin 5-HT_2 receptor (Trichard et al 1998). As indicated in Table 1, amisulpride has demonstrated as much atypicality as the 5-HT_2/D_2 drugs, despite being a selective $D_{2/3}$ antagonist (Carriere et al 2000; Coukell et al 1996; de Lima et al 1999; Freeman 1997; Lecrubier 2000; Loo et al 1997; Paillere-Martinot et al 1995; Peuskens et al 1999; Puech et al 1998; Rein et al 2000; Speller et al 1997), and a recent controlled study comparing risperidone and amisulpride in more than 200 patients did not find any significant differences (Peuskens et al 1999).

This does not rule out the possibility that 5-HT_2 antagonism perhaps may have a beneficial role in atypicality in domains such as mood and cognition; however, current data suggest that 5-HT_2 receptors are neither unique nor necessary or sufficient to obtain atypical antipsychotic effect.

The Dopamine D_4 Hypothesis

The notion that the dopamine D_4 receptor may be involved in the action of atypical antipsychotics gained popularity based on two findings: clozapine's greater D_4 versus D_2 affinity (Van Tol et al 1991) and elevated D_4 in the brains of individuals with schizophrenia (Seeman et al 1993). Several pieces of evidence question the role of D_4 in either of these contexts of atypicality, however. First, typical drugs such as haloperidol and fluphenazine actually have a higher affinity for the dopamine D_4 receptor than clozapine (Schotte et al 1996). In addition, two drugs, one specific for the dopamine D_4 receptor, L-745,870 (Bristow et al 1997) and another selective for D_4 and 5-HT_2 (fananserin; Truffinet et al 1999), have not shown an antipsychotic effect. Finally, there are atypicals such as quetiapine that show insignificant affinity for the dopamine D_4 receptor, suggesting that D_4 is not unique (cf. haloperidol), necessary (cf. amisulpride, quetiapine), or sufficient for atypicality.

Table 1. Comparison of Multireceptor Antipsychotics (Risperidone, Olanzapine, and Quetiapine) with Amisulpride[a]

Therapeutic dimension	5HT_2/D_4 and D_2 (risperidone, olanzapine, quetiapine)	D_2 only (amisulpride)
Equivalent efficacy to typicals for positive symptoms	yes	yes
Less EPS than high doses of typicals (e.g., 10–20 mg haloperidol)	yes	yes
Better than high dose haloperidol for negative symptoms	slightly	slightly
Primary efficacy for affective symptoms	initial evidence	initial evidence[b]
Efficacy in "negative-symptom-only" schizophrenia	not tried	yes[b]
Relapse prevention with long-term treatment	yes	yes

EPS, extrapyramidal side effects.

[a]Amisulpide is a relatively specific $D_{2/3}$ blocker. The references for the amisulpride data are presented in the text.

[b]Amisulpride is effective in negative-symptom-only patients at lower doses than those required in the more conventional patients with a mixed positive–negative picture.

Low Affinity and Fast Dissociation from the D_2 Receptor

We recently proposed that the factor that can best account for atypicality is the faster dissociation rate (k_{off}) from the dopamine D_2 receptor, which results in a lower overall affinity for the dopamine D_2 receptor (Kapur and Seeman 2001). This proposal reconciles one of the earliest findings by Meltzer and colleagues, that is, lower affinity at the dopamine D_2 receptors with atypicals (as noted above) and a suggestion by others (Hartvig et al 1986; Seeman and

Tallerico 1998) that atypicals are distinguished by "loose" binding. This raises the question of how a lower affinity and a faster dissociation at the dopamine D_2 receptor may be responsible for atypical effects. In the case of dopamine D_2 receptors, a lower affinity is driven largely (>95%) by a faster dissociation from the dopamine D_2 receptor (Kapur and Seeman 2000). Antipsychotics do not differ significantly in the rate at which they attach to the receptor, but primarily in the rate at which they dissociate from the dopamine D_2 receptors (Kapur and Seeman 2000).

Drugs with lower affinity and faster dissociation often are given at higher doses. Thus, faster dissociation by itself does not mean a lesser effect on the dopamine D_2 system. One could, in principle, give a proportionally higher dose of a fast k_{off} drug and obtain exactly the same (or even a higher) level of equilibrium occupancy; however, even under circumstances of equivalent equilibrium occupancy, drugs with a faster dissociation exhibit different behavior under physiologic conditions. Regardless of fast or slow dissociation, all drugs depress tonic dopamine transmission to a degree determined by their overall occupancy (Kapur and Seeman 2001); however, drugs with a faster dissociation are much more responsive to phasic bursts of dopamine transmission. Because phasic transmission is essential for dopamine to exert its physiologic effects, drugs with a faster dissociation should attenuate dopamine transmission with lesser distortion of phasic physiologic signaling. This may account for the fact that antipsychotics with a faster dissociation from the dopamine D_2 receptor may lead to an antipsychotic effect with few or minimal EPS or prolactin elevation, decreased cognitive impairment, and perhaps greater improvement in secondary negative symptoms.

Although this hypothesis may explain the current antipsychotics and the atypicality that has been achieved, it does not explain why drugs such as clozapine show a preferential effect in refractory patients. Thus, there may be two facets to atypicality. The core features (i.e., no or few EPS, lack of prolactin elevation, and some preferential effects on negative symptoms and cognition) may be related to a more judicious effect at the dopamine D_2 receptors via a faster dissociation. The effects on refractory symptoms, however, may require the involvement of some other receptors. It is important to distinguish a fast k_{off} and a rapid decline in occupancy, as measured by positron emission tomography (PET). The former is a molecular property of how the antipsychotic interacts with the receptor in the presence of dopamine in a seconds-to-minute time frame. The second—that is, decline as measured by PET—is a measure of how system level "bulk" occupancy declines as a function of time, measured in hours and days, and mainly determined by brain kinetics. Although we have proposed that the former— that is, a fast k_{off} at the molecular level—is important for atypicality (Kapur and Seeman 2000, 2001), the precise role of the second factor (i.e., the rate of decline of system level occupancy) is not as yet clear. The fact that compounds with fast dissociation from the D_2 receptor are effective antipsychotics (e.g., clozapine and quetiapine; see next section) gives rise to an important question: Do dopamine D_2 receptors have to be blocked 24 hours a day? If not, which seems to be the case, there are profound implications for future antipsychotic development.

Atypical Antipsychotics: Receptor Occupancy Findings

Studies of Typical Antipsychotics

The advent of neuroimaging has made it possible to investigate the receptor occupancy of antipsychotics in patients while they are treated. The usefulness of this was first demonstrated by Farde et al (1988), who showed that most antipsychotics, with the exception of clozapine, showed high (70% and above) D_2 occupancy at usual clinical doses. The data also suggest that those who experienced EPS had higher levels of D_2 occupancy (Farde et al 1992). This suggestion has been replicated in several uncontrolled studies (Broich et al 1998; Scherer et al 1994) and confirmed in two controlled clinical studies examining the effects of dopamine D_2 occupancy on response and side effects using raclopride (a selective D_2/D_3 antagonist; Nordstrom et al 1993) and haloperidol (Kapur et al 2000a). The essential findings are similar: a lower level of occupancy (in the 65–70% range, when measured with ^{11}C-raclopride) is associated with antipsychotic response, whereas a higher level of D_2 occupancy (in the range of 80% and above) is associated with EPS. Thus, it is theoretically possible with conventional antipsychotics to obtain a clinical response without EPS, although this therapeutic window is rather narrow and subject to wide interindividual variation. Although it is tempting to speculate that nonresponders (to high doses of antipsychotics) may have some resistance to the D_2 occupancy by the antipsychotics, it has been shown that they do not differ from responders in terms of D_2 occupancy (Wolkin et al 1989). It is also to be noted that there is a distinct temporal dissociation between receptor occupancy (which takes at most a few hours) and clinical response (which accrues gradually over days; Kapur et al 2000a). This delay in the antipsychotic response suggests that other factors, such as changes at the second messenger level or evolution of psychological processes, intervene between the blocking of dopamine D_2 receptors and the eventual expression of antipsychotic effect.

Studies of Atypical Antipsychotics

Clozapine is the prototypical atypical antipsychotic and has now been extensively investigated using PET (Farde and Nordstrom 1992; Kapur et al 1999; Nordstrom et al 1995). At very low doses (50 mg/day), less than what is routinely required for antipsychotic effect, it shows complete occupancy of the serotonin 5-HT_2 system (Kapur et al 1999), even though it is not an effective antipsychotic at this dosage. Clozapine's antipsychotic efficacy, at least in refractory patients, is best seen in the range on 300–400 ng/mL, a level at which its D_2 occupancy is in the range of 50 to 60% (Kapur et al 1999; Nordstrom et al 1995). Although controlled comparative studies are not available, all the published data suggest that clozapine's D_2 occupancy, at least at the time points measured, is lower than that of typical antipsychotics, lower than that of risperidone and olanzapine, and lower than the threshold required for EPS or prolactin elevation. This low level of D_2 occupancy, therefore, is the simplest—and perhaps only—explanation required to explain why clozapine does not give rise to EPS and sustained prolactin elevation (Farde and Nordstrom 1992; Kapur et al 1999).

Although a modest D_2 occupancy may be sufficient explanation for clozapine's lack of EPS and sustained prolactin elevation, clozapine's efficacy in refractory patients still remains unclear. Indeed, recent evidence suggests that even patients who do not respond to olanzapine (a drug that most closely replicates clozapine's multireceptor profile), show a good response to clozapine (Conley et al 1999). Because both olanzapine and clozapine share a similar, and high, affinity for many receptors, it is unlikely that these receptors contribute to this differential efficacy. Three ideas are useful as one thinks of a possible differential efficacy in refractory patients. First, there are insufficient data on this issue, and most of the studies to date involving truly refractory schizophrenia have involved clozapine. Should its superiority continue to be demonstrated, then differences between it and other atypical drugs need to be sought. Various candidates can be proposed at this time: glutamate, noradrenaline, and dopamine D_1; however, there currently is little convincing evidence to focus on any of these. Because the difference in efficacy is notable only in a subgroup of patients, it is possible that some subtle difference in the way in which these drugs interact with the dopamine D_2 system may also be relevant. For example, whereas both olanzapine and clozapine block the dopamine D_2 receptors, clozapine differs from olanzapine in having a much faster dissociation from the dopamine D_2 receptor and much faster pharmacokinetics, thus providing a different profile of receptor blockade.

Clozapine may be the gold standard, but it should not be regarded as unsurpassable. It is possible that clozapine's low D_2 occupancy, although beneficial in many ways, may also be a mechanism that is not fully exploited. A recent double-blind controlled study increased D_2 occupancy in a group of clozapine partial responders by adding sulpiride to their treatment. There was significant improvement in positive and negative symptoms when compared with placebo augmentation, suggesting the low D_2 occupancy of clozapine might also represent a weakness in certain situations (Shiloh et al 1997). Having said this, augmenting clozapine with further D_2 antagonism comes at a cost. Another investigation adding low dose haloperidol to ongoing clozapine treatment reported an increase in D_2 occupancy from 55 to 78%; however, this was accompanied by prolactin elevation into the abnormal range (Kapur et al 2001).

Thus, although clozapine's effects on D_2 receptors may explain a part of atypicality (i.e., few EPS, low prolactin elevation, fewer secondary negative symptoms and, perhaps, decreased cognitive impairment), it is not as easy to explain its superior efficacy in refractory patients.

Risperidone becomes an effective antipsychotic at a level of D_2 occupancy conventionally seen with typical antipsychotics, that is, at doses of 2 mg, it exhibits 60% or greater D_2 occupancy (Kapur et al 1999). High levels of $5HT_2$ occupancy are observed even at these lower doses (Farde et al 1995; Kapur et al 1999). Risperidone is remarkable for a high incidence of prolactin elevation, even higher than what is predicted by its central levels of D_2 occupancy (Lavalaye et al 1999). The precise reason for this is not known, but from cellular and animal model studies (Bowden et al 1992) it can be inferred that risperidone (or its metabolites) have relatively less blood–brain barrier penetration. To achieve the requisite level of in-brain D_2 occupancy required, drugs which cross the blood–brain barrier poorly will lead to proportionally much higher plasma and pituitary D_2 blockade levels, explaining this disproportionately high prolactin elevation.

Olanzapine also shows a preferential blockade of serotonin $5HT_2$ as compared with the dopamine D_2 receptors (Kapur et al 1998; Nyberg et al 1997); however, it becomes an effective antipsychotic only at doses that give rise to 60 to 70% dopamine D_2 blockade (around 10 mg per day for most patients; Kapur et al 1998; Nordstrom et al 1998). In the dose range of 10–20 mg per day, its D_2 occupancy is within the range of 65 to 80%; however, at doses of 30 mg per day and above, it tends to give rise to occupancy above 80%, and there is a suggestion of greater prolactin elevation and EPS in the $>$ 30 mg/day range (Kapur et al 1998). Diminshed EPS with olanzapine, even at higher levels of D_2 occupancy, may be related to its high affinity for cholinergic receptors (Schotte et al 1996), although in vivo this property seems to be somewhat muted (Raedler et al 2000; Zhang and Bymaster 1999).

Quetiapine, like clozapine, risperidone, and olanzapine, exhibits a higher level of $5HT_2$ than dopamine D_2 occupancy at all clinical doses studied (Gefvert et al 1998; Kapur et al 2000b); however, even at doses of 450 to 600 mg/day, its D_2 occupancy is in the rather low range (i.e., $< 30\%$ 12 hours after last dose). Although this finding by itself may challenge the importance of D_2 blockade in its antipsychotic efficacy, recent examination of the time course of D_2 occupancy with quetiapine shows that it gives rise to a higher D_2 occupancy (45 to 60%) in the time period immediately after administration. It then declines rather rapidly, as predicted by its fast pharmacokinetics during the interdose interval (Gefvert et al 1998; Kapur et al 2000b). Like clozapine, its low level of D_2 occupancy may explain its very low risk of EPS and prolactin elevation. This also may explain why doses of 150 to 300 mg per day show questionable efficacy (Small et al 1997). In fact, the dose of quetiapine required to reach 60 to 70% occupancy during peak would be 600 mg per day or above. Because the relationship between D_2 blockade and clinical response is not immediate, is it necessary to block dopamine D_2 receptors 24 hours a day? (Kapur et al 2000b). This transiently high occupancy that characterizes both clozapine and quetipaine may account for the reports of rapid relapse in patients who discontinue these medications (Seeman and Tallerico 1999).

Amisulpride, unlike the other atypicals reviewed here, does not have affinity for the serotonin $5HT_2$ receptors (Trichard et al 1998). Doses of amisulpride between 600 and 900 mg/day achieve 70 to 80% D_2 occupancy, whereas doses $>$ 1100 mg/day result in $> 85\%$ D_2 occupancy (Martinot et al 1996). Amisulpride shows an optimal balance between efficacy and diminished risk of EPS in the 400 to 800 mg/day range (Freeman 1997), as would be expected from its D_2 occupancy. At higher doses, EPS are observed in a dose-dependent fashion. Amisulpride has been shown to be effective in patients with primarily negative symptoms at low doses, in the range of 100 to 300 mg/day (Loo et al 1997; Paillere-Martinot et al 1995). These doses would be expected to give rise only to low levels of D_2 occupancy (in the 20–30% range). This raises the question of whether low levels of other medications (e.g., 1 mg haloperidol, 5 mg olanzapine) would also be effective in this patient population.

What Makes an Antipsychotic "Atypical"? A Short Summary

We propose that at present the definition of atypicality should read something like this: a drug that improves the psychotic/positive and negative symptoms of schizophrenia, with minimal or no EPS, and with minimal or no sustained prolactin elevation. The enhanced efficacy on positive and negative symptoms is not a universally achieved attribute among atypicals.

What then leads to an atypical antipsychotic? We propose that a blockade of dopamine D_2 receptors with a drug that shows a relatively (compared with haloperidol) low affinity and fast dissociation from the dopamine D_2 receptor at a molecular level and is prescribed at a dose that leads to less than 80% D_2 occupancy will lead to an "atypical" antipsychotic effect. This need not be the only mechanism to obtain atypical antipsychotic effect, hopefully, there will be many alternative pathways to the same clinical end: However, as we have reviewed above, it is perhaps the mechanism that has been realized in the current generation of atypicals. According to our thinking, the multireceptor profiles are not necessary and are not sufficient by themselves unless they are paired to include a component of appropriate D_2 blockade.

Is there any role for non-D_2 receptors in treating schizophrenia? Absolutely. Psychosis is only one aspect of schizophrenia. Although psychosis in schizophrenia (and perhaps in some other illnesses) can be linked with some certainty to dysregulated dopamine transmission, the primary cause for this dysregulation is not yet clear. Furthermore, schizophrenia is likely a complex polygenetic illness, beset with affective, cognitive, behavioral, and functional limitations. The illness precedes psychosis and evolves over time. It is likely and perhaps inevitable that as our understanding of schizophrenia improves and as the pathophysiology of the nonpsychotic symptoms of schizophrenia becomes clear, non-D_2 strategies will come to have very defensible roles in the treatment of schizophrenia, in and beyond psychosis. Nonetheless, whether the current multireceptor profiles are indeed the ideal ones remains an open question.

Linking Pathophysiology and Therapeutics: A Heuristic Model

To help integrate the foregoing ideas about antipsychotics with the current ideas about the etiology and pathophysiology of schizophrenia, we provide a simple model illustrated in Figure 1. This is a heuristically useful, rather than an empirically verified, model but has the virtue of integrating etiopathogenesis, phenomenology, and therapeutics. Although the etiology of schizophrenia is unknown, a number of genes and environmental factors are likely to be implicated—to differing degrees in different patients (event 1 in Figure 1). It is not possible to list all the genes implicated or the plethora of environmental factors that are associated with risk, but it would be fair to conclude that schizophrenia as we know it is unlikely to be

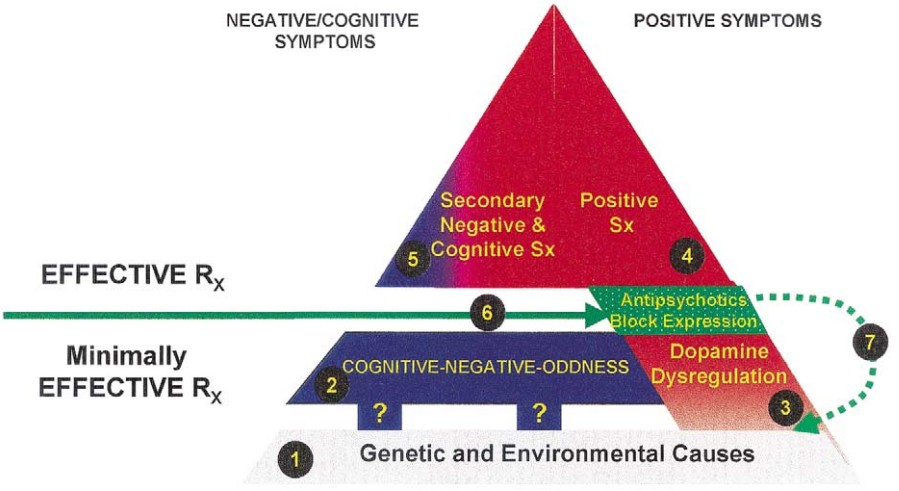

Figure 1. The figure depicts a heuristic model to link the pathophysiology of schizophrenia to its current treatment strategies. The numbers reflect the chronological order of events and processes. The text provides a description of the model. Rx, medication; Sx, symptoms. The figure is reprinted, with permission, from Annual Reviews of Medicine, Volume 52, ©2001 by Annual Reviews.

a single-gene or single-hit disorder. Several competing ideas on this issue recently have been catalogued elsewhere (Heinrich 2001). Whatever the precise antecedents, they lead to deficits well before psychosis is evident. These deficits can be identified years before the first episode of psychosis in incidental records of home videos (Walker et al 1993), school ratings and social measures (Ellison et al 1998), army screening records (Rabinowitz et al 2000), as well as in prospective psychological studies (Poulton et al 2000). These abnormalities are seen not only in the cognitive but also the social and behavioral domains (Ellison et al 1998; Poulton et al 2000; Rabinowitz et al 2000; Walker et al 1993). These deficits are not specific and are difficult to prospectively distinguish from the normal variance of children and youth; not every patient with schizophrenia displays them. On the basis of current evidence, however, one can be reasonably certain that these "cognitive-negative-social deficits" (event 2 in Figure 1) precede the onset of psychosis and constitute a risk for the development of subsequent schizophrenia. A similar antecedent subclinical phase has been suggested by Meehl (1962, 1989) and more recently by Tsuang and colleagues (Faraone et al 2001; Tsuang et al 2000) under the term *schizotaxia.* If this is all that the patient exhibits, it is not as yet schizophrenia, and he or she does not yet require psychiatric intervention.

It is proposed that at some point in late adolescence or early adulthood, a dysregulated hyperdopaminergic state superimposes on this picture (event 3 in Figure 1). This has been documented in imaging studies to constitute a picture of increased dopamine synthesis (Lindstrom 1998; Reith et al 1994), dysregulated release (Abi-Dargham et al 1998; Breier et al 1997; Laruelle et al 1996) and higher than normal levels of endogenous dopamine (Laruelle et al 1999). This dysregulated hyperdopaminergia, particularly in the mesolimbic system, is what expresses itself as psychosis (Miller 1984, 1989; 1989). The hyperdopaminergia and the psychosis are probably state phenomenon that are superimposed on the longitudinal course of schizophrenia (Laruelle et al 1999; event 4 of Figure 1). This dopamine dysregulation and the attendant psychosis also lead, perhaps secondarily, to negative and cognitive symptoms (event 5 of Figure 1). It is the superimposition of psychosis on the otherwise nonspecific picture of cognitive-negative-social-deficits that requires psychiatric intervention and determines a diagnosis of schizophrenia.

Antipsychotics remain the mainstay of the treatment of schizophrenia, and all antipsychotic treatments function primarily by blocking dopamine D_2 receptors (Kapur and Seeman 2001). We contend that atypical antipsychotics also are effective because they block dopamine D_2 receptors, although they are "atypical" in the way they do it (event 6 of Figure 1). This interruption of the expression of dopaminergic dysregulation leads to a resolution of symptoms that lie above the therapeutic line in Figure 1, but it does not fundamentally change the underlying pathologies. In fact, there is limited evidence that treatment with dopamine blockers fundamentally changes the course of the illness. There is some suggestion that prolonged antipsychotic treatment via factors such as depolarization block (Grace et al 1997) leads to a restitution of the dopaminergic dysregulation (as exemplified by event 7 in Figure 1), but convincing proof for the validity of this is lacking in humans. In any case, even if prolonged remission of illness by medications changes the underlying causes for dysregulation, these changes are not enduring

because nearly 50% of patients relapse within 6 months of discontinuing their medications (Gilbert et al 1995).

"All Models Are Wrong, Some Models Are Useful."

The heuristic model presented here is an obvious oversimplification; however, it should put into perspective some important conceptual points. First, antipsychotics—even the atypical ones—are merely anti-*psychotic*, not anti-*schizophrenic*. In fact, they are as efficacious for psychosis in other conditions as they are for the psychosis of schizophrenia. Second, the model suggests that the dopaminergic dysregulation is, in all likelihood, a secondary consequence of some other more primary pathophysiology. Current treatments block the behavioral consequences of hyperdopaminergia and will remain limited until the underlying primary pathophysiology is identified and targeted. Third, the model points out that the negative-cognitive-oddness spectrum may have a pathophysiologic basis distinct from that of psychosis. Thus, hopes of an ideal anti-*psychotic* that will erase these symptoms is probably mislaid. Treatment of these symptoms may require therapeutic axes distinct from those embodied in the current antipsychotics.

If this model is even partially right, it would suggest that we should conceive of schizophrenia not as multifaceted expression of a single pathophysiology, but as a collection of distinct pathophysiologies, each of which expresses itself in patients to varying degrees. In keeping with this idea, the ideal treatment will not be a single drug with multireceptor blockade ("one-size-fits-all" polypharmacy) but will require several specific and targeted treatment strategies that are titrated to match the variable expression of illness in each patient.

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