Understanding antipsychotic "atypicality": a clinical and pharmacological moving target

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The introduction of a number of new antipsychotics in the last decade has generated considerable excitement regarding the treatment of schizophrenia and related psychotic conditions. Clinically, it has produced changing expectations regarding treatment outcome, while academically it has encouraged a re-evaluation and expansion of theories of the pathophysiology of schizophrenia and antipsychotic activity. In this review, the development of antipsychotics is traced, beginning with chlorpromazine's introduction in the early 1950s, and followed to the present. Despite 50 years of use and a plethora of antipsychotics available worldwide, our conceptualization of their major mode of action remains essentially unchanged. It was shortly after their development that attention turned to the importance of dopamine, and in particular the dopamine D_2 receptor. Current thinking has elaborated on this model, with serotonin and glutamate receiving the greatest attention most recently, but D_2 antagonism remains the *sine qua non* of antipsychotic activity. Although the notion of "atypical" remains somewhat of a moving target, we do have at our disposal a new generation of antipsychotics that reflect a different clinical profile from their conventional counterparts. The precise degree of these differences and the underlying mechanisms remain unclear, however. The direction new antipsychotic development takes will undoubtedly hinge on answers to these questions.

Au cours de la dernière décennie, l'introduction d'un certain nombre de nouveaux antipsychotiques a -suscité beaucoup d'enthousiasme dans le traitement de la schizophrénie et des troubles psychotiques connexes. Dans le contexte clinique, ces nouveaux médicaments ont entraîné une évolution des attentes relatives à l'issue du traitement, tandis que dans les milieux universitaires, ils ont favorisé la réévaluation et l'enrichissement des théories de la pathophysiologie de la schizophrénie et de l'action antipsychotique. Cette étude décrit le développement des antipsychotiques de l'introduction de la chlorpromazine, au début des années 1950, jusqu'à aujourd'hui. Bien qu'il y ait pléthore d'antipsychotiques disponibles à l'échelle mondiale et qu'on utilise ces médicaments depuis 50 ans, la façon dont nous concevons leur principal mode d'action demeure essentiellement la même. Peu de temps après le développement des antipsychotiques, on a prêté attention à l'importance de la dopamine, et plus particulièrement au récepteur dopaminergique D_2. Les réflexions actuelles s'articulent autour de ce modèle. Si, récemment, on a accordé le plus d'attention à la sérotonine et au glutamate, l'antagonisme du récepteur D_2 demeure le préalable absolu de l'activité antipsychotique. Encore que la notion «d'atypique» demeure insaisissable

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dans une certaine mesure, nous disposons d'une nouvelle génération d'antipsychotiques reflétant un profil clinique différent de celui de leurs équivalents classiques. Ceci dit, le degré de différence exact et les mécanismes sous-jacents ne sont toujours pas clairs. Il ne fait aucun doute que le développement des nouveaux antipsychotiques sera fondé sur les réponses à ces questions.

Historical perspective

Even a decade ago, this type of review would have had a different message. Clozapine was only beginning to -re-enter the clinical market here in North America — what we had at that time was a number of antipsychotics that had evolved out of a model that identified dopamine, and in particular the D_2 receptor, as the critical component in psychosis.[1,2] There was a simple distinction between compounds as a function of this theory's development; low-potency antipsychotics characterized the early years when the mechanisms underlying their antipsychotic response were unclear, whereas a shift to high-potency agents occurred with our increased understanding regarding dopamine's putative role. There was no compelling evidence to suggest that any one of these compounds demonstrated clinical superiority,[3] and differences were really confined to side-effect profiles and issues related to their practical use.[4,5]

At that time, treatment focused on controlling positive symptoms (e.g., delusions, hallucinations). Our limited success in managing positive symptoms, even with these antipsychotics, encouraged ongoing work in this area, and the notion of pharmacological treatment of other symptoms was really just beginning.[6] Depot formulations were developed to contend with poor response related to noncompliance,[7] and the use of high-dose strategies gained popularity by the 1980s (e.g., rapid neuroleptization), perhaps more out of frustration than supportive evidence.[8–10]

Clozapine and the second-generation antipsychotics

The 1990s saw the most significant shift in the treatment of schizophrenia since the advent of chlorpromazine some 40 years earlier. After an extended hiatus related to a cluster of deaths in the early 1970s (later linked to agranulocytosis), clozapine was reintroduced in a number of countries for clinical use.[11,12] It was already clear at this point, highlighted by several unique attributes, that clozapine was not another "me too" antipsychotic; it showed diminished extrapyramidal side effects (EPS), clinical superiority in the treatment of refractory psychosis and the possibility of a broader spectrum of clinical efficacy (i.e., improvement in negative as well as positive symptoms).[13]

Why was clozapine atypical? Having a compound with these unique clinical features demanded a review of our thinking regarding the pharmacological mechanisms underlying schizophrenia. An agent that could prove clinically superior to already existing highly selective D_2 antagonists called into question the focus on dopamine and the D_2 receptor. What pharmacological aspects of clozapine accounted for its clinical benefits when compared with conventional antipsychotics? Clozapine's complex pharmacological profile[14] (Table 1) provided a number of possibilities, with at least several garnering particular attention.

D_1 receptor

Clozapine demonstrates greater affinity for the D_1 than the D_2 receptor.[14] This feature gains importance when viewed in the context of evidence indicating that D_1 receptors are predominant in the prefrontal cortex, an area critical to cognitive tasks,[19] implicated in negative symptoms[20] and hypothesized to play a key role in a feedback loop mediating more caudal structures associated with the positive symptoms.[21] D_1 and D_2 receptors interact at a cellular level, suggesting that D_1 antagonism might at the very least play a role through modulating D_2 activity.[22–24]

Although this latter point cannot be ruled out on the basis of current evidence, clinical trials with selective D_1 antagonists failed to support their role as effective antipsychotics per se.[25–27]

D_4 receptor

Clozapine's profile of greater D_4 versus D_2 affinity,[28,29] in combination with evidence that D_4 receptors were elevated in the brains of individuals with schizophrenia,[30] gave rise to an interest in the D_4 receptor. The initial enthusiasm has been tempered, however, by challenges to the latter finding,[31,32] as well as clinical trials with

selective D_4 antagonists that did not indicate effective antipsychotic activity.[33]

Dopamine and serotonin

One component of clozapine's pharmacological profile that garnered a great deal of attention was its greater 5-HT_2 versus D_2 binding, both in vitro and in vivo.[34–36] Meltzer and colleagues proposed that atypicality might be predicted by this particular feature,[34,37] and it soon became an attribute sought in the development of emerging antipsychotics. At present, most atypical antipsychotics available in North America (clozapine, olanzapine, quetiapine, risperidone, ziprasidone), in addition to sertindole (withdrawn from the market for reasons related to cardiac side effects) and zotepine, share this particular feature.[38] Amisulpiride, a selective D_2/D_3 antagonist,[39,40] is an exception to this rule, as is aripiprazole.

Re-visiting the dopamine-serotonin model

Dopamine's role in psychosis has been well established, but what do we know about serotonin and, specifically, the 5-HT_2 receptor?

First, evidence that selective serotonin antagonists are effective antipsychotics has not been forthcoming.[41,42] Furthermore, positron emission tomographic (PET) data have demonstrated that 5-HT_2 occupancy approaches saturation even at very low doses of atypicals such as clozapine, risperidone and olanzapine,[43] but the clinical reality is that higher doses are required to be effective as antipsychotics. Of course, neither of these findings rule out the possibility of a primary effect on other clinical dimensions, such as affect or cognition, or modulation of systems more directly involved in psychosis (i.e., dopamine).

Table 1: Central receptor affinity profile for clozapine*

Receptor	Relative affinity
Dopamine D_1	++
Dopamine D_2	+
Dopamine D_3	—
Dopamine D_4	++
Serotonin 5-HT_1	++
Serotonin 5-HT_{2A}	+++
Serotonin 5-HT_{2C}	++
Serotonin 5-HT_6	++
Serotonin 5-HT_7	++
α_1-Adrenergic	++
α_2-Adrenergic	++
Muscarinic M_1	+++
Histamine H_1	++

+ = low; ++ = intermediate; +++ = high.
*Adapted from references 15–18.

The work of Meltzer et al[34,37] did not, in fact, suggest serotonin antagonists in and of themselves would be effective antipsychotics. The model was premised on greater 5-HT_2 than D_2 activity, and went so far as to suggest that a 5-HT_2/D_2 ratio of 1.12 and above (based on pK_i values for cortical 5-HT_2 and striatal D_2 binding sites) characterized atypical antipsychotics.

Indirect support for the importance of greater 5-HT_2 versus D_2 activity comes from PET in vivo data. Loxapine has equal 5-HT_2 and D_2 binding[44] and takes on a typical profile in the clinical setting. Similarly, compounds such as olanzapine and risperidone lose this profile in a dose-dependent fashion. That is, occupancy of 5-HT_2 receptors approximates saturation even at lower therapeutic doses, but as the dose is increased, D_2 occupancy rises and ultimately overrides the differential that existed at lower doses.[36,45,46] In both cases, this results in an increased risk of EPS, albeit to a greater extent in risperidone, which lacks any inherent anticholinergic activity.[47]

That virtually all atypicals currently available for clinical use (including clozapine, olanzapine, quetiapine, risperidone, zotepine and ziprasidone) share this profile of greater 5-HT_2 versus D_2 antagonism, offers further indirect support for this model. However, amisulpiride, a selective D_2/D_3 antagonist, also claims atypical status,[38,48] as did remoxipride, a selective D_2 antagonist,[49] before its withdrawal because of an associated risk of aplastic anemia. Thus, a combined dopamine–serotonin profile as outlined may provide atypicality, but it cannot be considered necessary or sufficient in this regard.

Fast off the D_2 receptor: an alternative model

A feature that *all* currently available antipsychotics, typical as well as atypical, share is that of D_2 antagonism. In contrast to selective 5-HT_2 antagonists, selective D_2 antagonists have proven to be effective antipsychotics; taken together, the evidence would suggest that D_2 blockade is the *sine qua non* of antipsychotic

activity. At the same time, it cannot be sufficient, as we can see refractory forms of psychosis even in the face of significant D_2 antagonism.[50,51]

An interesting twist has arisen more recently with the notion of a differential blockade of D_2 receptors,[52–55] on both the molecular and systemic levels. Regarding the former, in vitro studies have demonstrated that antipsychotics dissociate from the D_2 receptor at very different rates, expressed as a k_{off} value. As a group, the atypicals have higher k_{off} values, that is faster dissociation rates, than the conventionals, but they differ among themselves on this dimension as well (e.g., quetiapine > clozapine > olanzapine).[53,54]

Systemically, the principle is similar, but other variables must be factored into the equation as well (e.g., half-life and k_{off}). In vivo PET data have demonstrated that plasma kinetics do not mirror CNS kinetics. For example, after a single dose of risperidone, the mean plasma half life for risperidone plus 9-OH-risperidone is 10.3 hours, but the mean half life for striatal D_2 occupancy is 66.6 hours.[56]

What are the implications of this model? It is well known that dopamine is required for a number of functions (e.g., movement, affect, cognition),[57] and it is possible that its role in normal functioning may be less disturbed by compounds that do not cause sustained D_2 blockade. At a molecular level, antipsychotics with higher k_{off} values are better able to decrease their occupancy in response to increased dopamine surges required for task-related activities. At a systems level, the net result includes only transient prolactin elevation and a diminished D_2 up-regulation with continued administration.[52,53] Clinically, it can be argued that many of the benefits ascribed to the second-generation antipsychotics reflect this profile of transient rather than sustained D_2 antagonism. This would include decreased EPS (and therefore secondary negative symptoms), in addition to decreased affective and cognitive disturbances.

Other models

In the last decade, much of our attention regarding "atypicality" has been focused on dopamine and serotonin, and they continue to be the subject of investigation. Work on serotonin has largely focused on the 5-HT_{2A} receptor, but more recent attention has turned to other serotonergic receptors in terms of both clinical response and side effects.[47,58–61] For example, the 5-HT_{1A} receptor has been implicated in anxiety, depression and negative symptoms, whereas the 5-HT_{2C} receptor has been linked to weight gain and improvement in EPS. In terms of dopamine, the role of the D_3 receptor, if for no other reason than its location in limbic regions, remains intriguing but poorly understood.[62–64] As discussed earlier, the predominance of D_1 compared with D_2 receptors in the prefrontal cortex, their apparent interactive roles and the prominent D_1-binding properties of clozapine, all contribute to an ongoing interest in this particular receptor.

Aripiprazole, recently approved for clinical use in the United States, offers an interesting variation on the dopamine and serotonin story. What makes it particularly unique among the newer antipsychotics is its partial dopamine agonist properties.[65] It demonstrates both 5-HT_{1A} agonism and 5-HT_2 antagonism, although its affinity for the D_2 receptors exceeds that for serotonin by an order of magnitude. Thus, it does not conform to the standard 5-HT_2/D_2 model. The drug has a very high affinity for the D_2 receptor and hence is unlikely to be fast k_{off}. Similarly, it has a long half-life and is therefore unlikely to be transient at a systemic level. Initial occupancy studies indicate that although it occupies more than 90% of dopamine receptors, aripiprazole does not cause EPS, suggesting that its inherent agonism may provide a mechanism that protects against excessive blockade of the D_2 system.[66] Although clearly not fast off the D_2 receptor, a parallel can be drawn in that both mechanisms of action provide appropriate modulation of D_2 transmission at the receptor level.

There is abundant reason to look beyond dopamine and serotonin, but such an expansive review is beyond the scope of this article; for this, the reader is referred to other sources.[67–69] The one system warranting comment on the basis of the amount of attention it is currently receiving is glutamate.[65,70–72] A strong argument for a glutamate model arises from the fact that phencyclidine (PCP), a psychotomimetic street drug, noncompetitively blocks the ion channel of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor. This model does not contradict a role for dopamine; for example, one action of dopamine is to inhibit glutamate release. Thus, a state of dopaminergic hyperactivity could lead to NMDA receptor hypofunction, which in turn could produce various symptoms linked with psychosis. To date, work with compounds acting at the level of the NMDA receptor (e.g., D-cyclo-

serine, glycine), have reported modest benefits in the treatment of positive symptoms, with more compelling evidence favouring effectiveness in treating negative and cognitive symptoms.[73–78]

Second-generation antipsychotics: the clinical evidence

To better evaluate the clinical evidence, schizophrenia must be seen as more than a unitary disease entity. Individuals undergoing a first psychotic episode are not the same as those in later stages of the illness. For example, they are more susceptible to certain side effects, such as acute dystonic reactions, but at the same time demonstrate a high rate of clinical response.[79–81] At this time in first-episode psychosis, there is a lack of evidence to suggest that atypicals are superior to their conventional counterparts, although this conclusion is drawn in the face of several caveats. With a response rate as high as 80%,[80] there is a kind of "ceiling effect" in place, making it difficult to distinguish differences between treatments. In addition, historically clinical trials have focused on response as measured along a small number of dimensions. For many years, the focus was confined to positive symptoms, before attention turned to a positive–negative symptom dichotomy. There is now evidence that a variety of other dimensions warrant investigation, including clinical measures (e.g., cognition, affect, quality of life) and side effects (e.g., weight gain, diabetes).[82] We are now only beginning to systematically evaluate some of these areas, and it is quite possible that as this evidence accumulates we shall see differences between the typicals and atypicals uncovered. Of course, it is important to qualify that the advantage could work in both directions.

Using response as a means of classification, it is also useful to distinguish between "partial responders" and those with "refractory" (also referred to as treatment-resistant) schizophrenia.[82–85] Partial responders best typify the population sampled for the pivotal clinical trials used for registration, that is individuals who have already received antipsychotic therapy, frequently with at least several agents, but who continue to demonstrate a sub-optimal response. Several large meta-analyses have been published evaluating these types of trials, and their findings are similar. Geddes and associates[86] concluded that atypicals offer modest clinical benefits compared with conventionals (usually represented by haloperidol or chlorpromazine in the trials). However, these benefits were lost when a distinction was made between those who received doses of the comparator below 12-mg haloperidol equivalents (in fact, it could be argued that the comparator doses were still too high). Evidence from a variety of sources has established that much lower doses of conventional antipsychotics than what have been used in the past are often sufficient to achieve clinical response. Moreover, these lower doses are associated with fewer side effects and better tolerability.[8,10,87–90] Having said this, data indicate that even at low doses the conventional antipsychotics can demonstrate a notable liability for EPS.[91–93]

The meta-analysis of Leucht et al[94] did not make this same distinction on the basis of dose, but it too concluded that the benefits of the atypicals in terms of total, positive and negative symptoms were modest at best. The most robust evidence favouring the atypicals was with respect to EPS, using antiparkinsonian drug use as a proxy. Again though, this meta-analysis did not attempt to address dose in the same fashion as Geddes et al.[86] Both meta-analyses acknowledged the lack of data currently available to evaluate the other clinical dimensions now receiving more attention.

The refractory or treatment-resistant population presents somewhat different findings. Dating back to the work of Kane et al[13] evaluating clozapine's efficacy in this sample, more rigid criteria have been used to distinguish these individuals from those who are better described as partial responders.[13] The existing evidence suggests modest benefits favouring the atypicals, with the additional caveat that clozapine seems superior even to the other atypicals in this population.[95–98]

Again, it must be emphasized that these conclusions are limited by the available data. We are only beginning to more objectively evaluate differences on other dimensions (e.g., cognition, suicide, subjective response, quality of life), and it is possible that further advantages may be claimed on some of these other measures (Table 2). Conversely, we are also aware that the newer agents have problems that were less of an issue with the conventionals, and in any comparison these cannot be overlooked. Here, in particular, reference is made to the mounting evidence regarding increased risk of weight gain, diabetes and possible secondary cardiovascular complications.[99–103]

With so many dimensions, in terms of efficacy as well as side effects, the concept of "atypicality" is called into question. Should we expect that an atypical antipsychotic be superior on all dimensions to warrant

this classification? Clozapine, the prototype of atypical antipsychotics, was initially identified as unique because of its lack of D_2-related adverse events (i.e., EPS, hyperprolactinemia), features that characterized existing antipsychotics at the time. Only later did attention turn to its possible benefits along other clinical dimensions. Even using this more restrictive definition related to EPS and elevated prolactin, there are problems. Risperidone, for example, is routinely classified as atypical, although it has been clearly associated with elevated prolactin and increased risk of EPS in a dose-related fashion.[104–107] It is not so surprising then that recent discussions have turned to the topic of correct terminology to describe these newer agents,[108] or that the suggestion has been made that these compounds be best viewed in a dimensional rather than dichotomous fashion strictly tied to a typical–atypical classification.[109]

Future directions

It is somewhat ironic that in the face of so much excitement during recent years about gains in our understanding of schizophrenia and its treatment, we return dopamine to centre stage. Less than 10 years ago, clozapine was being held forth as evidence that a compound with relatively low D_2 occupancy could be an effective antipsychotic, calling into question the integral role of D_2 antagonism in the action of antipsychotics.

A closer examination of clozapine, particularly through the benefits of in vivo imaging, has clarified this issue, refining rather than dismissing existing notions regarding the importance of D_2 activity. Clozapine's D_2-binding profile does not negate data suggesting a relation between D_2 thresholds, clinical response and side effects. Rather, it has demonstrated that sustained D_2 occupancy is not necessary for antipsychotic effectiveness. Moreover, compounds that dissociate from the D_2 receptor quickly may bestow benefits along a number of clinical dimensions (e.g., cognitive, affective and negative symptoms), in addition to a lack of D_2-related side effects.

Table 2: Proposed advantages of atypical antipsychotics over typical antipsychotics

Symptoms[16,18,110–113]	Side effects[86,94,98,114–118]	Outcome[16,98,110,119–123]
Positive	EPS/TD	Response rate
Negative	CNS morphology	Refractory psychosis
Cognitive	Hyperprolactinemia	Suicide
Affective	Tolerability	Functional recovery
Aggression	Compliance	Quality of life
		Health care costs

Note: EPS = extrapyramidal side effects; TD = tardive dyskinesia.

A critic of this explanation might argue that we can still not be sure that clozapine's D_2 activity plays a role in its antipsychotic action. However, to date there is no evidence indicating that a compound without some degree of D_2 binding can act as an effective antipsychotic. There is, in fact, pre-clinical data indicating that altering clozapine's D_2 property transforms it into a standard conventional antipsychotic.[124]

Our understanding of clozapine is incomplete though, for it remains unclear why it is superior in refractory psychosis, even when compared with other atypicals. That it relates to its D_2 profile of rapid dissociation would gain support from evidence that a drug such as quetiapine shares the same clinical advantage. Evidence of this sort with quetiapine has not been forthcoming however, although it must be acknowledged that there exists a paucity of data involving quetiapine's use in this population. Clozapine's pharmacological profile has been closely scrutinized in an effort to unlock this secret, and at one time or another hopes have been pinned on 5-HT_2, D_1 and D_4 activity. Selective antagonists for each of these receptors have simply confirmed that at least individually they are not responsible for clozapine's unique clinical profile. This does not rule out their involvement — it merely suggests that the net effect of clozapine may be dependent on some complex interplay between its different pharmacological actions.

In a sense it can be argued that we are back to square one. In truth, we have no better understanding of clozapine's superiority in refractory psychosis than we did a decade ago, and we have come full circle to the realization that D_2 blockade is essential for antipsychotic activity. In the ongoing search, though, we have learned a great deal. Consolidating the existing evidence, we can state the following:

- dopamine antagonism is a necessary, but not sufficient, requirement for antipsychotic efficacy
- sustained D_2 occupancy is not necessary to achieve this
- there is no evidence that other systems can produce a primary antipsychotic action
- other systems may influence antipsychotic activity through modulating dopamine activity
- other systems may play a primary role on other clinical dimensions related to the illness (e.g., affect, cog-

nition), although at present this remains conjecture

Our excitement regarding clozapine was magnified by evidence that improvement occurred across numerous clinical dimensions — not only did it not cause EPS or sustained hyperprolactinemia, it improved positive, negative, cognitive and even affective symptoms. It is not so surprising then that efforts to develop other effective antipsychotics were accompanied by the expectation that an antipsychotic must simultaneously do many things beyond just treating psychosis. This, in turn, has fostered the development of compounds that also affect numerous receptors and systems; however, it is time to question this position.

I close with a rather contrary position regarding clozapine. Yes, it appears superior in refractory psychosis (though recently the degree and domains of this superiority have been challenged), and we should continue our search to understand whatever gains it gives us. Efforts so far to establish a unitary explanation have failed, and it is easy to imagine that the answer lies in some interaction of its rich pharmacology. Continuing to develop such pharmacologically complex compounds, however, makes it extremely difficult to tease apart the critical feature(s) underlying its benefit.

What if, instead of its rich pharmacology, much of clozapine's benefits in the other realms simply reflect what it doesn't do? Using Parkinson's disease as a model, we know that sub-optimal dopamine functioning can adversely influence not only movements, but other features clozapine is seen to be superior in "treating," including cognition, affective disturbances and negative symptoms. It is easy to ascribe these benefits to different pharmacological features of clozapine, when they may simply reflect its lack of sustained D_2 occupancy. The decreasing superiority of atypicals over typicals when more appropriate doses of the latter are being used for comparison purposes supports this position, as does the evidence that amisulpride, a selective D_2/D_3 blocker, emulates almost all the features in Table 2. Of note is the more recent finding that amisulpride shares in common with clozapine rapid dissociation from the D_2 receptor.[53]

If clozapine's benefits along these other clinical dimensions can be explained by its dopamine-sparing properties, we may be misguided in (a) looking for a single pill to address the complex symptom profile of schizophrenia when we all agree that the illness is heterogeneous and multidimensional; (b) trying to link the different benefits noted with clozapine to different aspects of its diverse pharmacology, and in so doing (c) continuing the practice of synthesizing complex molecules to mirror clozapine on these different clinical measures.

Perhaps we should focus on finding a better *antipsychotic*, leaving it to others to continue the search for better antidepressants, anxiolytics, cognitive enhancers and so on. It will then be the clinician's job to use the different agents flexibly and appropriately in the service of a particular patient's illness.

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