D_2 and 5-HT_2 Receptor Effects of Antipsychotics: Bridging Basic and Clinical Findings Using PET

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The advent of a number of new antipsychotics has been paralleled by efforts to better delineate their mechanisms of action and, in doing so, further our understanding of schizophrenia and its pathophysiology. Technological advances, such as positron emission tomography (PET), have proven to be powerful tools in this process, allowing us to evaluate in vivo models based primarily on in vitro evidence. Combined serotonin-2/dopamine-2 (5-HT_2/D_2) antagonism represents one such model, and we now have PET evidence available that can be extrapolated to our understanding and clinical use of both conventional and novel antipsychotics. *(J Clin Psychiatry 1999;60[suppl 10]:15–19)*

The pharmacologic feature of combined serotonin-2/dopamine-2 (5-HT_2/D_2) antagonism has played a critical role in efforts to explain the clinical properties of the second generation antipsychotics. While other biochemical factors have also been implicated in the pathophysiology of schizophrenia and its treatment,[1] it is notable that greater 5-HT_2 versus D_2 activity represents the one feature shared in common by all novel, "atypical," or second generation antipsychotics currently approved for clinical use in North America (i.e., clozapine, olanzapine, quetiapine, and risperidone) as well as others presently under investigation or approved elsewhere (e.g., sertindole, ziprasidone, zotepine).[2]

This article offers a brief review of earlier in vitro evidence supporting this particular model, followed by an overview of more recent in vivo evidence employing positron emission tomography (PET).

COMBINED 5-HT_2/D_2 ANTAGONISM AND "ATYPICALITY": IN VITRO FINDINGS

Clozapine, the prototype of atypical antipsychotics, quickly became identified as having unique features in the clinical setting,[3] although it was unclear as to what accounted for these properties. However, in vitro work by Meltzer and colleagues[4,5] provided evidence to indicate that atypicality may be defined by the characteristic of greater 5-HT_2 versus D_2 antagonism. Indeed, work with a number of compounds suggested a specific ratio of 5-HT_2/D_2 pK_i values in this respect (≥ 1.12), which could be used to predict an agent's potential for atypicality in the clinical setting.[3,4] It is noteworthy that loxapine, an antipsychotic historically categorized within the conventional group, approximated this ratio as well, suggesting that it too may manifest at least some of the clinical benefits attributable to this feature. Also of note was the finding that amoxapine, a tricyclic dibenzoxazepine used as an antidepressant, appeared to fit this model of atypicality,[4,5] giving rise to the notion that it might have the potential for atypical antipsychotic features.[6]

CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS: IN VIVO EVIDENCE USING PET

It is now possible, employing PET, to corroborate and perhaps extend earlier in vitro findings. In doing so, there is an opportunity to better understand the clinical profiles of both conventional and novel antipsychotics.

Haloperidol

The synthesis of haloperidol heralded the high-potency class of conventional antipsychotics. Indeed, the search for highly selective D_2 antagonists was fueled by the hypothesis that schizophrenia reflected a disorder of hyperdopaminergic activity, with the D_2 receptor most closely associated with antipsychotic response.[7]

More recent evidence from our group, as well as the work of others, indicates that antipsychotic response is as-

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sociated with D_2 antagonism exceeding 60%[8,9]; conversely, exceeding a threshold of 80% leads to a marked increase in risk of extrapyramidal symptoms (EPS).[10] Moreover, it has been established that nonresponders do not demonstrate lower levels of D_2 occupancy,[11,12] arguing against the notion that higher doses will convert nonresponders to responders. Thus, a threshold between 60% to 80% D_2 occupancy appears to represent the optimal range to effect antipsychotic response while minimizing risk of EPS.

The level of D_2 occupancy associated with hyperprolactinemia may further narrow this threshold. Occupancy greater than 50% has been associated with hyperprolactinemia,[13] although preliminary work at our PET center has suggested that risk is associated with levels greater than 72%.[14]

Evidence with haloperidol indicates that the aforementioned thresholds represent a rather narrow dose range. Haloperidol at 1 mg falls below an average occupancy of 65%, although by 2.5 mg this level is exceeded.[8,15] Moreover, haloperidol at 5 mg exceeds the noted thresholds for hyperprolactinemia and EPS.[15,16] These findings dovetail nicely with earlier clinical evidence indicating that even in acute treatment there is a lack of evidence to indicate that doses in excess of 12 mg/day offer superior benefit,[17] as well as with more recent evidence that even doses lower than 12 mg/day may be as effective.[18–20] Unfortunately, haloperidol is largely devoid of 5-HT_2 antagonism, thereby failing to gain the clinical benefits associated with such blockade.

Clozapine

A striking finding with clozapine has been its relatively low D_2 activity, reported in a number of studies to be in the range of 20% to 67%.[10,21] Indeed, even doses at the high end of the therapeutic range fail to lead to a substantial increase in D_2 occupancy, suggesting a "glass ceiling" to describe the relationship between dose and D_2 occupancy and implying the possible involvement of other pharmacokinetic factors.

In combination with this profile of relatively low D_2 activity is higher concomitant 5-HT_2 antagonism, with occupancy in the range of 85% to 90%, even at doses of 125–200 mg daily.[21] To this extent, the in vivo profile of clozapine closely parallels what was predicted based on earlier in vitro evidence.

Risperidone

Unlike clozapine, risperidone demonstrates a profile of D_2 occupancy more in keeping with conventional agents such as haloperidol.[22,23] It exemplifies the importance of corroborating in vitro findings with in vivo evidence, as in vitro work clearly predicted atypicality clinically.[24–26] Although risperidone does manifest relatively higher 5-HT_2 activity at therapeutic doses, e.g., 2 to 6 mg daily, the 5-HT_2 activity approaches saturation as the dose is increased, allowing concomitant D_2 occupancy to continue increasing and "override" the potential benefits of the associated 5-HT_2 activity.[22,23,27,28] Risperidone's risk of EPS demonstrates this phenomenon. At lower doses, the risk is no greater than that with placebo; however, as the dose is increased, risk of EPS rises and even begins to approximate that of haloperidol.[29,30]

This finding suggests that a threshold exists with combined 5-HT_2/D_2 antagonism and that benefits attributable to serotonergic activity may be diminished or even lost at the point where 5-HT_2 antagonism of the serotonergic system reaches saturation while D_2 blockade continues to increase.

Olanzapine

Olanzapine is similar to risperidone in demonstrating relatively high D_2 occupancy at therapeutic doses, i.e., greater than 70% at doses of 10 mg/day. It too has high 5-HT_2 activity at those doses and, like risperidone, it can approach saturation of the 5-HT_2 receptors at higher doses while D_2 occupancy continues to rise.[31,32] The fact that EPS seem less of an issue with olanzapine versus risperidone at comparatively higher therapeutic doses is thought to reflect, at least in part, its added antimuscarinic activity,[33] a feature devoid in risperidone.[34]

Quetiapine

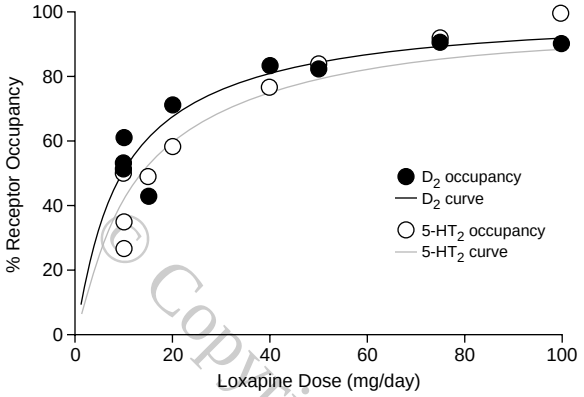
Like clozapine, and unlike risperidone and olanzapine, quetiapine has relatively low D_2 antagonism. Indeed, evidence to date suggests that its level of D_2 activity is even less than that of clozapine at its recommended therapeutic doses,[35,36] and in this sense it appears to parallel clozapine in terms of a "glass ceiling" with respect to D_2 occupancy. Once more, this attribute may reflect these compounds' capacity to bind "loosely" to the D_2 receptor. In keeping with this argument, both clozapine and quetiapine cause only transient increases in prolactin elevation,[37,38] and the ability of quetiapine to be detected at the level of the D_2 receptor following drug administration is considerably shorter than for its 5-HT_2 occupancy.[39]

Unlike clozapine, risperidone, and olanzapine, though, quetiapine's 5-HT_2 antagonism, while comparatively higher than its D_2 blockade, is not as great as that seen with these other compounds, and even at higher therapeutic doses its occupancy is well below saturation.[36]

Loxapine and Amoxapine

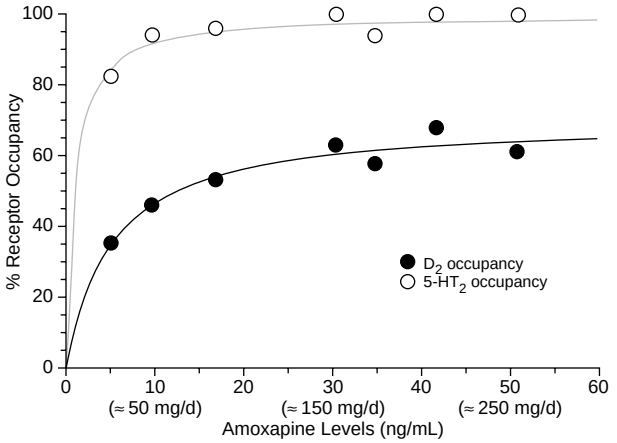
Loxapine, like risperidone and olanzapine, has higher D_2 occupancy at therapeutic doses. In addition, though, it has high 5-HT_2 occupancy at these doses that approximates its degree of D_2 antagonism (Figure 1) and distinguishes it from other conventional agents such as haloperidol.[41] Evidence from PET corroborates the recommendation of a relative potency relationship of 15:2 for loxapine:haloperidol,[42] and also indicates that doses in the

Figure 1. Receptor Occupancy for Dopamine D_2 as Measured With [^{11}C]Raclopride and for 5-HT_2 Using [^{18}F]Setoperone in 10 Patients on Stable Doses of Loxapine[a]



[a]From reference 41, with permission.

Figure 2. Receptor Occupancy for Dopamine D_2 as Measured With [^{11}C]Raclopride and for 5-HT_2 Using [^{18}F]Setoperone in 7 Patients on Stable Doses of Amoxapine[a]



[a]Adapted from reference 40, with permission.

range of 15 to 30 mg can achieve D_2 occupancy within the threshold range of 60% to 80%.[43]

Although not classified as an antipsychotic, amoxapine fits the model of atypicality defined by in vitro findings,[4,5] and more recent PET data (Figure 2) indicate that the profile of greater 5-HT_2 versus D_2 activity is demonstrated in doses at least as high as 250 mg daily.[40] It is of interest that amoxapine has been suggested to have antipsychotic properties clinically,[44] although this has never been systematically evaluated.

A CLASSIFICATION SYSTEM FOR ANTIPSYCHOTICS BASED ON 5-HT_2/D_2 OCCUPANCY

All models are wrong; some models are useful.

—Deming, "Guide to Stella"

Taken together, current PET evidence can be used to construct a classification system based on the conceptual framework of 5-HT_2/D_2 antagonism (Table 1).[45,46]

The precise implications of such a model remain unclear at present. On the one hand, it may provide a means of distinguishing antipsychotic compounds based on a framework of 5-HT_2/D_2 occupancy, a feature that, as noted earlier, is shared by all the newer antipsychotics currently available in North America. At the very least, it offers a testable hypothesis for comparing and contrasting the various agents' clinical and side effect profiles.

Having said this, to suggest that such a model can be entirely comprehensive in its explanation is somewhat naive. Just as the theory that schizophrenia is related solely to hyperdopaminergic activity is rather simplistic, it is likely that a 2-neurotransmitter model, although extending our understanding, is also likely to be overly simplistic. The fact that several other transmitters are also affected by these newer agents gives rise to a number of other potential explanations, and there are already other classification systems that have incorporated this in the form of more complex models.[47,48]

Table 1. Classification of Antipsychotics Based on Relative Serotonin-2/Dopamine-2 (5-HT_2/D_2) Occupancy at Clinically Recommended Doses

5-HT_2/D_2 Classification	Antipsychotic
High D_2[a]/low 5-HT_2	Haloperidol
High D_2/high 5-HT_2[b]	Loxapine[c]
	Olanzapine
	Risperidone
Low D_2/high 5-HT_2	Clozapine
Low D_2/low 5-HT_2	Quetiapine

[a]High D_2: > 60%.
[b]High 5-HT_2: > 80% (and > D_2).
[c]Loxapine: D_2 > 60%; 5-HT_2 ≈ D_2.

DISCUSSION

While in vitro work reflects a basic starting point in understanding the pharmacologic profile of new compounds, the final arbiter is in vivo evidence. For various methodologic reasons, the former does not always extrapolate to the latter,[45] and PET offers a means of corroborating in vitro findings.

The impact can be felt at the level of clinical application as well. One such example is the more recent PET work associating levels of D_2 occupancy with clinical response and risk of EPS and hyperprolactinemia.[9–14] More specifically, it appears that compounds that call upon D_2 occupancy in order to effect their clinical response require occupancy beyond a threshold of 60% to 70%. Conversely, occupancy in excess of approximately 70% is associated with hyperprolactinemia, while levels greater than 80% are associated with a marked increase in the risk of EPS. These findings suggest that a relatively narrow threshold exists between clinical response and risk of ad-

Table 2. Dose Equivalents (mg) for Various Antipsychotics

Antipsychotic	Dose Equivalent Based on D_2 Occupancy	APA Guideline[42]
Haloperidol	2	2
Loxapine	15	15
Olanzapine	10	2–3
Risperidone	2.5–3	1–2

verse side effects. With a side effect such as EPS, concomitant 5-HT_2 antagonism may widen this threshold, but the effect is finite and can be diminished or even eliminated as D_2 occupancy is allowed to increase with the use of higher doses.

Another example involves the issue of treatment nonresponse. In the past, higher antipsychotic doses have frequently been employed in individuals failing to respond adequately to lower doses. From PET data involving D_2 occupancy, though, it has been demonstrated that nonresponders do not represent individuals who have not achieved adequate levels of occupancy, arguing against the position of simply pursuing higher and higher doses.

A further benefit arising from PET relates to the establishment of equipotent doses between agents, at least where D_2 activity is seen to account for their clinical response. At present, this would seem to hold true for all conventional agents as well as risperidone and olanzapine, whereas clozapine and quetiapine do not fit this conceptual model because of their relatively low D_2 blockade. Previous efforts to establish equipotent doses have been indirect and largely dependent on pharmacokinetic data, whereas PET offers a direct measure of receptor occupancy at the level of the central nervous system. It may be argued that PET data, at least to date, have been limited by the measurement of striatal, rather than mesolimbic, D_2 receptors, although the former appears to parallel mesolimbic D_2 occupancy.[49]

On the basis of PET evidence, we have been able to establish such comparative doses for compounds that have been the subject of investigation at our PET center. Incorporating data gathered from other centers is limited by methodologic issues that may qualify precise comparisons. Table 2 outlines suggested comparative doses for a limited number of compounds based on studies carried out at our center using similar methodologic approaches and the same ligands.

It is of note that these recommendations are at odds with other guidelines for dosing comparisons, e.g., those set out in the American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia.[42] It is our position that in vivo D_2 occupancy is the most precise means of establishing such guidelines, although this is once again said with the caveat that compounds exist that do not appear to require D_2 antagonism in the same fashion to establish antipsychotic response, i.e., clozapine and quetiapine.

This last point calls into question the interpretation of D_2 occupancy levels. Seeman and Tallerico[50] have raised the notion of "loose" and "tight" binding at the level of the receptor, and it may be necessary to incorporate this line of thinking to more fully understand PET results.

Finally, the PET data currently available provide yet another means of categorizing the growing number of antipsychotics available for clinical use. What are the implications of such an approach? At this point, it is unclear, but at the very least this information provides a framework for comparing these agents on a variety of clinical dimensions, e.g., dosing, clinical outcome, and side effects. It is also possible that these findings may serve to distinguish groups of compounds based on clinical efficacy, thereby adding considerably to our understanding regarding mechanisms of action and the respective roles of different systems in the symptoms of schizophrenia.

In summary, the use of PET has added considerably to our knowledge of the antipsychotics, both old and new, that we use to treat schizophrenia. In doing so, we have an opportunity to develop compounds with even greater effectiveness and tolerability, while at the same time gaining a better understanding regarding the pathophysiology of this illness.

Drug names: amoxapine (Asendin), clozapine (Clozaril), haloperidol (Haldol and others), loxapine (Loxitane and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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