Clinical and Theoretical Implications of 5-HT$_2$ and D$_2$ Receptor Occupancy of Clozapine, Risperidone, and Olanzapine in Schizophrenia

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Objective: Dopamine D$_2$ receptor occupancy measurements provide a valid predictor of antipsychotic response, extrapyramidal side effects, and elevation of prolactin levels. The new antipsychotics clozapine, risperidone, and olanzapine obtain antipsychotic response with few extrapyramidal side effects and little prolactin elevation. The purpose of this study was to compare the D$_2$ and serotonin 5-HT$_2$ receptor occupancies of these drugs in patients receiving multiple-dose, steady-state regimens. **Method:** Forty-four patients with schizophrenia (16 taking risperidone, 2–12 mg/day; 17 taking olanzapine, 5–60 mg/day; and 11 taking clozapine, 75–900 mg/day) had their D$_2$ and 5-HT$_2$ occupancies determined with the use of [^{11}C]raclopride and [^{18}F]setoperone, respectively, and positron emission tomography imaging. **Results:** Clozapine showed a much lower D$_2$ occupancy (16%–68%) than risperidone (63%–89%) and olanzapine (43%–89%). Risperidone and olanzapine gave equal D$_2$ occupancies at doses of 5 and 20 mg/day, respectively. All three drugs showed greater 5-HT$_2$ than D$_2$ occupancy at all doses, although the difference was greatest for clozapine. **Conclusions:** Clozapine, at doses known to be effective in routine clinical settings, showed a D$_2$ occupancy clearly lower than that of typical antipsychotics, while risperidone and olanzapine at their usual clinical doses gave the same level of D$_2$ occupancy as low-dose typical antipsychotics. The results also suggest that some previous clinical comparisons of antipsychotics may have been confounded by different levels of D$_2$ occupancy. Clinical comparisons of these drugs, matching for D$_2$ occupancy, may provide a better measure of their true "atypicality" and will help in understanding the contribution of non-D$_2$ receptors to antipsychotic effects.

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E$_{\text{very}}$ known antipsychotic blocks dopamine D$_2$ receptors. While this does not prove a causal relationship between D$_2$ blockade and antipsychotic response, the association between the two is undeniable. Thus, it is

of obvious interest to compare the relative D$_2$ receptor occupancies of the available antipsychotics. Farde and colleagues (1) proposed that one needs a "threshold" of D$_2$ occupancy to induce antipsychotic response. Prospective studies have largely confirmed this notion, although it is unclear whether this threshold is 60% or 70% and whether the threshold for inducing response is the same as the one for maintaining it (2, 3). Nonetheless, there is a mechanism of antipsychotic response that relies on D$_2$ occupancy alone (4). Furthermore, it has been noted that as D$_2$ occupancy increases, especially as it rises above 80%, the incidence of extrapyramidal side effects increases (1). Elevation of prolactin levels may also show a threshold relationship with respect to D$_2$ occupancy (5, 6, and unpublished data from our laboratory). While D$_2$ occupancy may be necessary for response, it is not always sufficient, as there are patients who do not respond despite adequate D$_2$ occupancy (7). However, it would be fair to claim that D$_2$ occupancy provides a reliable (and per-

haps the best) pharmacological predictor of response to antipsychotic medication, extrapyramidal side effects, and elevation of prolactin levels.

There are now several antipsychotics that have a lower propensity than typical antipsychotics to cause extrapyramidal side effects and prolactin elevation: clozapine, risperidone, olanzapine, sertindole, and quetiapine (8–12). The first three have been used most extensively in patients and are the focus of this study. Given the relevance of D_2 occupancy for response to antipsychotics, extrapyramidal side effects, and prolactin elevation, it is of obvious interest how these antipsychotics compare on this index. The main purpose of this study was to compare the D_2 occupancy of these three drugs in patients receiving multiple-dose, steady-state regimens of the drugs across their usual range of clinical use.

It has been suggested that drugs may demonstrate atypical clinical features (i.e., low extrapyramidal side effects and prolactin elevation) if they have at least a 10 times higher affinity for serotonin 5-HT$_2$ receptors than D_2 receptors in vitro (13, 14). In patients this translates into a preferential occupancy of 5-HT$_2$ receptors as opposed to D_2 receptors (15). Clozapine, risperidone, and olanzapine all show a higher affinity for 5-HT$_2$ receptors than D_2 receptors in vitro, but the amount by which 5-HT$_2$ exceeds D_2 is unclear. In animal tissue or cloned human receptors, clozapine shows a much higher 5-HT$_2$/D_2 ratio (20 times higher affinity for 5-HT$_2$ than for D_2) than either risperidone (11 times) or olanzapine (12 times) (16). On the other hand, occupancy measurements in rats following subcutaneous injection showed that risperidone had the highest 5-HT$_2$/D_2 affinity ratio (19 times) as compared with clozapine (5.1 times) and olanzapine (7.5 times) (16). Therefore, a second purpose of this study was to systematically compare the 5-HT$_2$ occupancies and the 5-HT$_2$/D_2 occupancy ratios in patients.

Several previous reports have presented data on one or two of these antipsychotics separately. However, these studies used different imaging modalities (positron emission tomography [PET; 17–21] or single photon emission computed tomography [SPECT; 22, 23]); different radioligands ([^{11}C]raclopride [17–20], [^{11}C]-NMSP [21], or [^{123}I]IBZM [22, 23]); and different image analysis models (cerebellum as reference [17–21] or frontal cortex as reference [22, 23]). As a result, it is not valid to compare the occupancy of, say, risperidone obtained with [^{123}I]IBZM SPECT to that of clozapine derived by using [^{11}C]NMSP PET. It is essential, when comparing drugs, that the data be obtained on all of the drugs in the same fashion. Furthermore, dose of a drug is a central determinant of its receptor occupancy, and some previous studies have compared occupancies without adequately controlling for dose (23). Any systematic comparison across drugs must compare not just the occupancy but also the dose-occupancy relationships over the clinically relevant dose range. To provide the first such comparison, we present data on the relation between dose, plasma level, and 5-HT$_2$ and D_2 oc-

cupancies in 44 patients with schizophrenia who were receiving a wide range of steady-state doses of clozapine, risperidone, and olanzapine.

METHOD

The procedures for this study were approved by the Human Subjects Review Committee of the University of Toronto. Patients participated after receiving detailed written information about the study and signing a consent document. Patients receiving ongoing treatment in our inpatient and outpatient clinic were recruited over a period of 4 years. We studied 44 patients (36 male and eight female) aged 19–54 years; 43 had a DSM-IV diagnosis of schizophrenia, and one had a diagnosis of atypical psychosis. Sixteen patients were receiving risperidone (2–12 mg/day), 17 were receiving olanzapine (5–60 mg/day), and 11 were receiving clozapine (75–900 mg/day). The patients were not randomly assigned to the three drugs, and the limitations of this are discussed later. Most of the patients were chosen from a clinic population so as to provide a representative range of doses for each drug, which is a sufficient study design for obtaining the in vivo 5-HT$_2$/D_2 profile of the three drugs in patients. However, because of inadequate prospective control over drug and dose assignment and the fact that patients were in various degrees of remission at the time of scanning, the design was limited in its ability to obtain reliable associations between receptor occupancy and clinical outcome. Nonetheless, to ensure a valid comparison of the action of the three drugs on the receptors, the patients in this report conformed to the following criteria.

1. All patients were on multiple-dose, steady-state levels (at least 5 days on the particular dose) of the medication for which they were assessed.

2. All patients were free of any confounding major medical or neurological illness. None of the patients had received any depot antipsychotics in the year before this PET examination, and none had received any other antipsychotics for a minimum of 14 days before the PET examination. None of the patients had concurrent substance abuse or substance dependence (nicotine excepted).

3. Patients were not receiving any other psychotropic medication that might confound the findings for D_2 occupancy, with the exception of benzodiazepines and/or an antiparkinsonian agent, as indicated in table 1. It has been shown that the addition of lorazepam does not alter the measurement of D_2 occupancy with [^{11}C]raclopride (24).

4. All patients received a scan for dopamine D_2 receptors, and most received a scan for serotonin 5-HT$_2$ receptors. All patients had their [^{11}C]raclopride PET examinations done 12–13 hours after their last nightly drug dose (the usual scan start was at 9:00 a.m.). The [^{18}F]setoperone PET examination for 5-HT$_2$ receptors, if done, followed the [^{11}C]raclopride examination on the same day and started 14–15 hours after the last nightly drug dose.

PET data on some of the patients have appeared in previous reports (19, 20); these patients are identified in table 1. To carry out a systematic comparison, data on all of the subjects in the study were analyzed (those reported before were reanalyzed) with the methods described below, and all patient data were compared with the same baseline data to eliminate any across-drug bias. As a result, there may be a slight variation in the occupancy reported here and that reported before.

The PET scans to estimate D_2 occupancy were obtained after the injection of 10 mCi of high specific activity [^{11}C]raclopride (300–1600 Ci/mmol) according to a bolus-plus-infusion protocol. The scanning methods used have been described in a previous report in this journal (2). The pertinent aspects are the following. Striatal and cerebellar regions of interest were drawn on two contiguous PET slices on a composite PET image with reference to a coregistered magnetic resonance imaging (MRI) scan (GE Signa 1.5-T scanner; T$_2$-weighted spin-echo sequence coregistered to the PET scan with a surface-matching algorithm). An estimate of the D_2 binding potential (D_2 BP) of raclopride (which represents the B_{max}/K_d of [^{11}C]-raclopride for D_2 receptors, where B_{max} is the total number of receptors available to a ligand, and K_d is the affinity of the ligand for the

TABLE 1. Relationship Between Drug Dose, Plasma Level, and D_2 and 5-HT$_2$ Receptor Occupancies in Subjects Taking Risperidone, Olanzapine, and Clozapine

Subject	Age (years)	Sex	Dose (mg/day)	Plasma Level (ng/ml)	Other Medications	D_2 Occupancy (%)	5-HT$_2$ Occupancy (%)
Risperidone group							
1[a]	36	M	2	17.4	Benzodiazepine	64	—[b]
2[a]	19	M	2	8.3	None	67	—[b]
3[a]	28	M	2	11.6	None	71	—[b]
4	24	M	2	21.5	None	63	72
5[a]	19	M	4	11.9	None	70	—[b]
6[a]	33	M	4	20.5	Benzodiazepine	79	—[b]
7[a]	24	M	4	15.7	None	74	—[b]
8[a]	20	M	4	19.8	Benzodiazepine	81	—[b]
9	45	F	4	21.5	None	76	~100
10	33	M	5	32.0	Benzodiazepine	79	96
11[a]	28	M	6	84.4	Benzodiazepine	85	—[b]
12[a]	20	M	6	17.1	None	73	—[b]
13	31	M	6	39.5	Benzodiazepine	81	~100
14	37	M	8	50.2	Benzodiazepine	82	~100
15	26	F	10	72.2	Thyroxine, benzodiazepine	89	95
16	20	M	12	71.0	Antiparkinsonian agent	87	97
Olanzapine group							
1[a]	25	M	5	8.9	Benzodiazepine	43	93
2[a]	24	M	5	15.8	Benzodiazepine	64	~100
3[a]	25	F	5	8.5	Benzodiazepine	59	91
4[a]	20	M	10	38.1	None	75	93
5[a]	38	F	10	19.7	Benzodiazepine	71	~100
6[a]	24	M	10	36.4	None	74	99
7	28	M	10	22.1	None	66	—[b]
8[a]	29	M	15	20.9	None	75	~100
9[a]	23	F	15	62.2	None	76	~100
10[a]	36	M	15	32.4	None	73	~100
11[a]	44	M	20	38.4	Benzodiazepine	74	~100
12[a]	30	F	20	29.6	None	76	~100
13[a]	19	M	20	37.5	None	80	~100
14[a]	21	M	30	78.4	Benzodiazepine and antiparkinsonian agent	84	—[b]
15[a]	25	M	30	61.0	None	82	—[b]
16[a]	24	M	40	181.5	Antiparkinsonian agent	88	—[b]
17	20	M	60	—[b]	None	89	—[b]
Clozapine group							
1	54	F	75	255	None	16	~100
2	25	M	150	107	None	28	97
3	37	M	200	191	Benzodiazepine	64	~100
4	20	M	250	427	None	53	—[b]
5	31	M	300	859	Benzodiazepine	60	90
6	24	M	350	394	None	64	~100
7	25	M	500	442	None	56	93
8	20	M	500	285	None	52	—[b]
9	36	F	600	430	None	65	~100
10	41	M	850	362	Benzodiazepine	47	~100
11	43	M	900	205	Benzodiazepine	68	~100

[a] Subject was reported on in previous articles (19, 20).
[b] Data not available.

receptors) was obtained from the ratio of the striatum to the cerebellum during the 30- to 75- minute interval, a period of prolonged pseudo equilibrium afforded by the bolus-plus-infusion protocol. As used in our laboratory, this method yields a test-retest standard deviation of 6% and has been standardized to have an interrater and intrarater reliability, as measured by the intraclass correlation coefficient (ICC-III), of >0.95.

To estimate receptor occupancy, we used an age-corrected baseline value derived from a pool of 16 normal subjects and 12 antipsychotic-naive patients with schizophrenia. Since the illness had no statistically discernible effect on D_2 receptors as measured with [^{11}C]raclopride in this sample (F=0.66, df=1, 25, p=0.42) and in a previous report by others (25), data from the antipsychotic-naive patients and normal subjects were pooled to provide a more robust effect of age on D_2 binding potential. Drug-induced D_2 receptor occupancy was determined as (D_2 BP$_{Base}$–D_2 BP$_{Drug}$)/(D_2 BP$_{Base}$), where

D_2 BP$_{Base}$ is the age-corrected D_2 baseline binding potential, and D_2 BP$_{Drug}$ is the D_2 binding potential for patients taking the antipsychotic drug. The absence of the patient's own baseline values introduces a potential error; the error as calculated on the basis of variance in the data from antipsychotic-naive persons is expected to vary from 0% to 9% for patients with 50% occupancy and from 0% to 4% for patients with 80% occupancy (26).

The 5-HT$_2$ scans were obtained with the use of a bolus injection of 5 mCi of high specific activity [^{18}F]setoperone (360–6210 Ci/mmol), according to the method developed and standardized by Blin et al. (27, 28). The 5-HT$_2$ occupancy was determined in the prefrontal cortex regions of interest drawn on the [^{18}F]setoperone scan with reference to a coregistered MRI (as described above). An index of the 5-HT$_2$ receptors was obtained from the prefrontal cortex/cerebellar ratio over the 65- to 90-minute time period. The cerebellum is practically devoid of 5-HT$_2$ receptors (29), and studies in baboons as

well as humans report no displaceable [^{18}F]setoperone binding in this region (27, 28, 30). It can be shown that at a time when the binding of the radioligand is at pseudo equilibrium, the prefrontal/cerebellum ratio represents 5-HT$_2$ BP + 1 (31). The details of this method as applied here have been described elsewhere (32). We have shown that this method yields an average test-retest deviation of 6%–7% and an acceptably high interrater reliability (ICC-III >0.95) (32).

Since these patients were already receiving treatment, it was not possible to measure their baseline 5-HT$_2$ binding potential. In the absence of this baseline, we used the age-corrected 5-HT$_2$ binding potential obtained from 11 antipsychotic-free patients with schizophrenia and 26 age-matched normal subjects. The pooling of normal subjects and patients results in a more robust age-corrected regression and is justified because there was neither a main effect of diagnosis (F=1.20, df=1, 33, p=0.28) nor a significant effect of diagnosis on the age regression (F=0.59, df=1, 33, p=0.45) (33). Occupancy was calculated in the same way as for dopamine D$_2$ occupancy.

The patients had blood drawn at the time of the D$_2$ PET scan; the samples were analyzed in batches by drug. Clozapine plasma levels were measured by means of high-performance liquid chromatography with electrochemical detection by a method based on previously published techniques (34). Risperidone plasma levels were measured by means of a radioimmunoassay for the active moiety, which reflects both risperidone and 9-OH risperidone, by the Janssen Research Foundation, Beerse, Belgium (35). Olanzapine plasma levels were measured by means of high-performance liquid chromatography with electrochemical detection by BAS Analytics (West Lafayette, Ind.).

Since the patients were, by design, taking the drugs at different dose and plasma levels, a direct comparison of the occupancies without reference to dose is not very informative. To provide a valid comparison, we characterized the dose-occupancy relationship for each drug and compared these profiles across the three drugs. The expected relationship between a drug level and occupancy of the receptors should conform to a rectangular hyperbola, assuming bimolecular (drug-receptor) interactions and negligible occupancy by the endogenous ligand. A rectangular hyperbola, in this context, is defined by equation 1:

$$\%Occ = Occ_{max} \times \frac{D_{Conc}}{ED_{50} + D_{Conc}} \, ,$$

where %Occ is the observed occupancy, Occ$_{max}$ is the theoretically maximum occupancy for that particular drug, D$_{Conc}$ is the amount of the drug (expressed either as dose or plasma level), and ED$_{50}$ is a constant equivalent to the amount of the drug required to occupy 50% of Occ$_{max}$. If there is reason to believe that all of the [^{11}C]raclopride can be displaced by the drug in question, Occ$_{max}$ can be replaced by 100 in equation 1. In its truest form, D$_{Conc}$ should represent the concentration of the drug in the synapse. Since there is no easy way to measure the synaptic concentration of the drug in patients, one can use dose and plasma level as functional surrogates. However, it should be kept in mind that dose and plasma level only indirectly reflect synaptic concentrations. Noncompliance with the medication regimen or changes in metabolism may lead to different plasma levels for a given dose, and there may be significant differences in the levels of the freely available drug in the synapse if there is a change in protein binding. The observed receptor occupancy was related to the administered dose and measured plasma level with the use of equation 1 implemented in SPSS for Windows (SPSS Inc., Chicago).

RESULTS

For all three drugs, increasing doses led to increasing plasma levels, consistent with expectations and affirming reasonable compliance (table 1). A simple comparison of the occupancies shows that clozapine had a significantly lower D$_2$ occupancy than risperidone and olanzapine (main analysis of variance, F=13.05, df=2, 39, p<0.001; post hoc comparison with risperidone: p<0.001; with

olanzapine: p<0.001), which were themselves indistinguishable (Tukey's honestly significant difference post hoc test, risperidone versus olanzapine: p=0.80).

The D$_2$ occupancies in response to increasing doses and plasma levels are presented in figure 1 and figure 2. In each case, a rectangular hyperbola provided a better fit (i.e., explained a greater degree of variance) than a simple linear fit. The parameters for the curves relating occupancy to dose were as follows: for risperidone, Occ$_{max}$=91%, ED$_{50}$=0.8 mg/day, with 77% variance explained; for olanzapine, Occ$_{max}$=92%, ED$_{50}$=3.2 mg/day, with 81% variance explained; for clozapine, Occ$_{max}$=71%, ED$_{50}$=112 mg/day, with 55% variance explained. The parameters for the curves relating occupancy to plasma level were as follows: for risperidone, Occ$_{max}$=88%, ED$_{50}$=3.2 ng/ml, with 59% variance explained; for olanzapine, Occ$_{max}$=90%, ED$_{50}$=6.4 ng/ml, with 84% variance explained; for clozapine, Occ$_{max}$=68%, ED$_{50}$=88 mg/day, with 18% variance explained. It is important to note that clozapine does not saturate the D$_2$ receptors, and the theoretical maximum occupancy (Occ$_{max}$) is 68%–71%. This is in contrast to risperidone and olanzapine, where we observed occupancies of up to 83% and where Occ$_{max}$ was 91% and 92%, respectively.

Curves relating dose and occupancy for risperidone and olanzapine had the same shape (a near-saturating rectangular hyperbola) and differed only in the dose axis. The amount of drug required to occupy 50% of the available D$_2$ receptors is 3.2 mg/day for olanzapine and 0.8 mg/day for risperidone if the equation is fitted with two parameters (and 4.5 versus 1.2 mg/day if Occ$_{max}$ is assumed to be 100%). This suggests that D$_2$-occupancy-equipotent doses of risperidone and olanzapine are in the ratio of 5:20 mg/day.

All three drugs showed a preferential occupancy of 5-HT$_2$ receptors versus D$_2$ receptors and the ability to completely occupy 5-HT$_2$ receptors, as measured by [^{18}F]setoperone (figures 1 and 2). The lowest doses tested—75 mg/day of clozapine, 2–4 mg/day of risperidone, and 5–10 mg/day of olanzapine—all led to more than 95% occupancy of frontal 5-HT$_2$ receptors in most patients. It should be noted that once occupancy goes beyond 90%, the signal available for analysis is less than 10%, and the precision of data beyond this point is limited. Since there were few patients who had midrange 5-HT$_2$ occupancies, it is not valid to try to fit the data to rectangular-hyperbola relationships. Nonetheless, clozapine possesses a greater degree of separation between its 5-HT$_2$ and D$_2$ occupancies than either risperidone or olanzapine (F=12.67, df=2, 25, p< 0.0002; clozapine was different at p<0.05, according to Tukey's post hoc unequal-N test, while risperidone and olanzapine were not different, p>0.10).

DISCUSSION

The data show that clozapine differs from risperidone and olanzapine in its D$_2$ occupancy profile. Ris-

FIGURE 1. Relationships Between Drug Dose and 5-HT$_2$ and D$_2$ Receptor Occupancies for Risperidone, Olanzapine, and Clozapine[a]
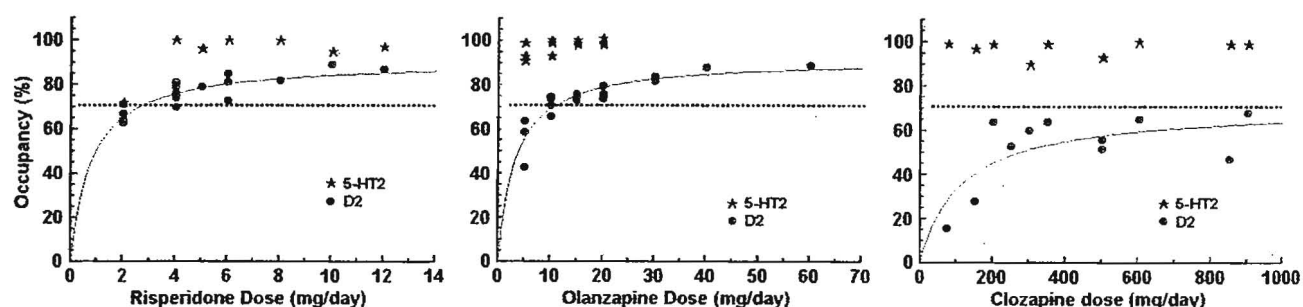
[a] The curves conform to equation 1 in the text. The horizontal line across the three graphs shows the theoretically maximum occupancy expected with the highest dose of clozapine. Even doses of 2 mg/day of risperidone and 10 mg/day of olanzapine gave higher occupancies than those expected with the highest dose of clozapine.

FIGURE 2. Relationships Between Plasma Drug Level and 5-HT$_2$ and D$_2$ Receptor Occupancies for Risperidone, Olanzapine, and Clozapine[a]
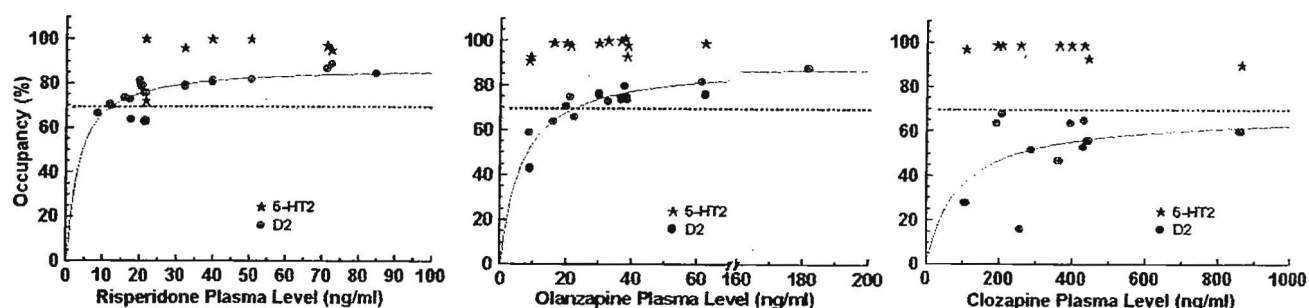
[a] The curves conform to equation 1 in the text. The horizontal line across the three graphs displays the theoretically maximum occupancy expected with the highest dose of clozapine. Levels of 10 ng/ml of risperidone and 20 ng/ml of olanzapine gave higher occupancies than those expected with the highest dose of clozapine.

peridone and olanzapine have similar profiles but differ in potency. All three of the antipsychotics are complete blockers of 5-HT$_2$ receptors, although clozapine shows the greatest difference between its 5-HT$_2$ and D$_2$ occupancies. We discuss how these findings relate to previous published work, discuss the limitations of our results, and then present the implications of these findings for comparisons between antipsychotics.

Differences in ligand selection, imaging modality, and analysis procedures make comparisons of numbers obtained by different centers difficult. Therefore, our results are best compared with those reported by groups that have data, at least on one of the two receptors, on all three drugs. Pilowsky et al. (23) compared the D$_2$ occupancies of clozapine, risperidone, and olanzapine using IBZM SPECT imaging. They concluded that the D$_2$ occupancy of olanzapine is statistically indistinguishable from that of clozapine and that the D$_2$ occupancy of risperidone is higher than that of both clozapine and olanzapine. Our data disagree with regard to olanzapine. The Pilowsky et al. study had several limitations. First, the spatial resolution, quantification, and signal/noise characteristics of IBZM SPECT imaging are inferior to those of [^{11}C]raclopride PET. Second, their study had a smaller total number of

subjects (N=22, versus N=44 in this study), a restricted dose range (10–20 mg/day for olanzapine, while we report on 5–60 mg/day), and fewer subjects taking olanzapine (six, while we report on 17). Third, Pilowsky et al. compared the occupancies without reference to the dose of the drug—the average dose for olanzapine patients was 12.5 mg/day, while that for risperidone patients was 8.7 mg/day, a confounding factor that might explain their finding of a lower occupancy for olanzapine and a higher one for risperidone (see below). Finally, they found no relation between dose and occupancy, questioning the internal consistency of the data. The present study overcomes these limitations.

The Karolinska PET group has provided data on a series of patients taking 125–600 mg/day of clozapine (18), four patients taking 6 mg/day of risperidone (17), and three normal control subjects taking a single dose of 10 mg/day of olanzapine (36). Our data on clozapine confirm theirs. We observed a maximal D$_2$ occupancy of 68%, and Nordström et al. (18) reported 67%; the theoretical maximum occupancy when plasma levels were related to D$_2$ occupancy was 68% in our study and 61% in theirs. Farde et al. (17) reported that 6 mg/day of risperidone led to 75%–80% D$_2$ occupancy; our data show an average of 79%

(range=73%–85%). Finally, on the basis of their study of single-dose olanzapine in normal volunteers, these investigators predicted that 10 mg/day of olanzapine should lead to 70% D_2 occupancy (36), which is consistent with our observed average of 72% (range= 66%–75%). Thus, our results are consistent with previous PET data and provide a more valid basis for comparison of the D_2 occupancies of the three drugs.

In addition, we made a comparison of the 5-HT$_2$ and D_2 occupancies of these drugs, which has never been reported before. It has been reported previously that low doses of clozapine lead to complete saturation of the 5-HT$_2$ receptors (18). The new finding here is that risperidone and olanzapine also completely block 5-HT$_2$ receptors. The results refute the findings of the occupancy studies in rats done by Schotte et al. (16) in which risperidone showed a greater separation of 5-HT$_2$ and D_2 occupancies. In our data, clozapine showed the greatest separation, with risperidone and olanzapine being similar.

Our study is not without its limitations. An important one is that the subjects were not randomly assigned to the drugs and to different doses of each drug. Since clozapine is used in patients who do not respond satisfactorily to other typical and atypical antipsychotics, there is a systematic selection bias here. While, clearly, a prospective randomized assignment to the three drugs would have been preferable, no study has yet been able to achieve this. Furthermore, while the clozapine patients do represent a more treatment-refractory group, there are no data to suggest that D_2 occupancy varies systematically as a function of lack of response; in fact, a previous study suggested that responders and nonresponders do not differ in D_2 occupancy (7). [^{11}C]raclopride provides only striatal D_2 occupancy. The exact site of antipsychotic response is not known, but it is speculated that the mesolimbic D_2 receptors may be crucial. However, it is worth noting that a recent study comparing striatal to mesolimbic D_2 occupancy, using [^{11}C]raclopride and [^{11}C]FLB (37), found no significant regional differences in D_2 occupancy between the striatum and the temporal cortex. It should be pointed out that preferential mesolimbic D_2 blockade is not a necessary precondition for mesolimbic selectivity. While there was no evidence for limbic selectivity of receptor blockade for any typical or atypical antipsychotics in ex vivo animal receptor occupancy studies (16), there is clear evidence for preferential functional antagonism of the limbic as opposed to the striatal dopamine system with several of the atypical antipsychotics (38).

Another limitation of our work, as of all the previous studies, is that the individual's own pretreatment binding potential was not available; therefore, the estimate of occupancy carries an inherent error. However, this error is likely to be small and randomly distributed (39). Furthermore, since the main focus of this study was the difference between the three drugs, all compared with the same baseline values, any such error is unlikely to account for the observed pattern of differences. Finally, it has been demonstrated in animals (40) and suggested in humans (5) that antipsychotics lead to an up-regulation of dopamine D_2 receptors. If so, a pretreatment baseline D_2 value may result in a lower estimate of D_2 occupancy. However, most animal data show that clozapine does not result in receptor up-regulation (40, 41), while the situation with respect to olanzapine and risperidone is not clear. Even if up-regulation occurs, it is more likely with risperidone and olanzapine than with clozapine, and this would have decreased, rather than increased, our chances of finding the difference we report.

What do these results tell us about the pharmacological mechanisms of antipsychotic action? Farde and colleagues (1) have suggested that one needs a threshold of D_2 receptor occupancy to obtain a satisfactory antipsychotic response. This threshold lies in the range of 65%–70% (2, 4). It is interesting, then, that both risperidone and olanzapine become effective antipsychotics only at doses which cross these levels of D_2 occupancy. Doses of risperidone and olanzapine that do not reach these levels (i.e., <2 mg/day of risperidone and <10 mg/day of olanzapine) are not reliably antipsychotic in most clinical situations. Clozapine, on the other hand, is able to obtain an antipsychotic response with levels of D_2 occupancy (usually 30%–60%) that would be insufficient to cause antipsychotic response by themselves (4). Thus, clozapine does not call on the typical D_2 occupancy mechanism for inducing antipsychotic response; risperidone and olanzapine do. This raises the possibility that despite some similarities in their receptor profile in vitro, the fundamental mechanism of response of clozapine may be different from that of olanzapine and risperidone in patients. While this question can ultimately be resolved only in a clinical arena in crossover studies, the data on D_2 occupancy provide a rationale for why patients who do not respond to risperidone/olanzapine may respond to clozapine and the other way around.

The 5-HT$_2$ receptor data show that all of these drugs are potent antagonists at that receptor. The fact that clozapine saturates 5-HT$_2$ receptors at such a low dose and that one continues to see an increasing response to clozapine in doses up to 350–400 mg/day (42) makes it unlikely that 5-HT$_2$ is the primary source of the antipsychotic effect of clozapine. A similar conclusion was reached by Trichard et al. (43) in their study of chlorpromazine and clozapine. It does not rule out the possibility that high levels of 5-HT$_2$ blockade may modulate or enhance the ability of D_2 blockade to induce response or to delay the onset of D_2-related side effects (14, 15). However, any benefit provided by a mixed 5-HT$_2$/D_2 model must express itself in a narrow range. Patients taking risperidone and olanzapine who have high D_2 occupancies experience extrapyramidal side effects and prolactin elevation despite a concomitantly high 5-HT$_2$ occupancy (19, 20).

These findings also raise interesting questions regarding the comparison of risperidone and olanzapine with each other and with typical antipsychotics. All of

the currently published "pivotal" studies that have compared olanzapine and risperidone with the reference drug haloperidol have used 10–20 mg/day of haloperidol (9, 10, 44). Thus, doses of olanzapine and risperidone that lead to 70%–80% D_2 occupancy have been compared with doses of haloperidol that result in more than 90% D_2 occupancy (3, 19). It is increasingly being realized that the optimal dose of haloperidol for treatment of most patients may be less than 6 mg/day, while higher doses may result in greater extrapyramidal side effects without extra efficacy (45). Since extrapyramidal side effects can also influence measurement of negative symptoms (46), this raises an interesting question: would risperidone/olanzapine demonstrate superior benefits for extrapyramidal side effects, prolactin levels, and negative symptoms if they were compared with a typical antipsychotic that has the same D_2 occupancy? Such D_2-occupancy-matched studies will be very valuable for discerning the true components of atypicality.

These data are also of interest in interpreting the comparison between risperidone and olanzapine. In a recently published trial (47), olanzapine, 17.2 mg/day, was compared with risperidone, 7.2 mg/day, and risperidone showed a higher propensity for extrapyramidal side effects and prolactin elevation. According to the equations derived from our data, the study compared an average of 77%–79% D_2 occupancy induced by olanzapine with an average of 82%–86% D_2 occupancy induced by risperidone. Because both extrapyramidal side effects and prolactin elevation are related to the amount of D_2 occupancy, and because as occupancy rises beyond 80%, extrapyramidal side effects become more prominent (1), this raises the question of whether the higher incidence of extrapyramidal side effects/prolactin elevation with risperidone is a function of the choice of dose (and resulting D_2 occupancy) rather than a qualitative difference between the two drugs. On the other hand, since the design of the Tran et al. study (47) permitted a clinical titration of the dose, it could also be true that olanzapine is able to muster a greater clinical response with a slightly lower level of D_2 occupancy (possibly because of the synergism of its multiple-receptor-blocking profile), and that if D_2-equipotent doses of risperidone and olanzapine were compared (e.g., 4–5 mg of risperidone versus 17.2 mg of olanzapine), risperidone might have lower extrapyramidal side effects/prolactin elevation, but olanzapine might then show superior efficacy.

In conclusion, this study provides the first systematic comparison of the D_2 and 5-HT$_2$ receptor occupancies of the three most commonly used atypical antipsychotics. Clozapine is able to induce an antipsychotic response with a D_2 occupancy lower than that of typical antipsychotics, and this may explain its freedom from extrapyramidal side effects and prolactin elevation. Risperidone and olanzapine become effective antipsychotics only when their D_2 occupancy is in the range obtained by low-dose typical antipsychotics (2, 3). They occupy equal numbers of D_2 receptors when used in the

dose ratio of 1:4 mg/day, respectively. All three drugs saturate the 5-HT$_2$ receptors at subtherapeutic doses, suggesting that 5-HT$_2$ occupancy alone is an unlikely explanation for their antipsychotic effects. The data also have implications for clinical comparison studies. Most studies comparing atypical antipsychotics with haloperidol have compared doses of risperidone/olanzapine that give 65%–80% D_2 occupancy with doses of haloperidol that give more than 90% D_2 occupancy. This may have biased these comparisons to produce higher extrapyramidal side effects and prolactin elevation with haloperidol. D_2-occupancy-matched trials of atypical antipsychotics versus haloperidol and atypical versus atypical antipsychotics would be more informative with regard to the true superiority of one drug over another and would also help in distinguishing the clinical role of receptors other than D_2.

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