Extrastriatal and striatal D2 dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia*

X. XIBERAS, J. L. MARTINOT, L. MALLET, E. ARTIGES, C. LOC'H, B. MAZIÈRE and M. L. PAILLÈRE-MARTINOT

Background Both traditional and atypical antipsychotics have been hypothesised to be effective in schizophrenia through limbic and cortical D2 dopamine receptor blockade.

Aims To investigate this hypothesis with the D2/D3-selective positron emission tomography (PET) probe [123I]FLB457.

Method PET scans were performed on 6 controls and 18 patients with schizophrenia treated with haloperidol or with risperidone, clozapine, amisulpride or olanzapine.

Results The D2 dopamine receptor blockade was high in the temporal cortex with both haloperidol and atypical antipsychotics. The atypicals, however, induced a significantly lower D2 binding index than haloperidol in the thalamus and in the striatum.

Conclusions Results suggest that cortical D2 dopamine receptors are a common target of traditional and atypical antipsychotics for therapeutic action. Higher in vivo binding to the D2 receptors in the cortex than in the basal ganglia is suggested as an indicator of favourable profile for a putative antipsychotic compound.

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Dopamine D2 receptor blockade is thought to mediate antipsychotic action. In vivo studies in medicated patients have shown that treatments with traditional antipsychotic compounds such as haloperidol consistently induce 70–80% occupancy of the striatal D2 receptors (Martinot et al., 1990; Nordstrom et al., 1993). Furthermore, high levels of D2 receptor occupancy in the striatum are associated with higher risk of extrapyramidal side-effects (Farde et al., 1992). At variance with traditional compounds, atypical antipsychotics such as clozapine have a lower tendency to induce extrapyramidal side-effects (Moller, 2000). This may be consistent with the lower in vivo D2 striatal blockade reported with the usual doses of clozapine (Farde et al., 1992). Whereas the nigro-striatal dopaminergic pathways appear to be involved in extrapyramidal side-effects, models of the antipsychotic mechanism of action involve extrastriatal cerebral structures such as the meso-cortico-limbic pathways (Moore et al., 1999). Therefore, the D2 receptor blockade by antipsychotic drugs in extrastriatal structures may be one of the mechanisms that account for the antipsychotic effect, as suggested by earlier single photon emission tomography studies (Bigliani et al., 2000; Stephenson et al., 2000). This hypothesis requires substantiation with the more sensitive and quantitative positron emission tomography (PET) technique. However, in the extrastriatal structures such as thalamus, limbic and temporal cortices, the D2 dopamine receptor density is 5- to 25-fold lower than in the striatal structures, where they exist in nanomolar concentrations (Kessler et al., 1993). The development of [123I]FLB457, a bromine-labelled benzamide radioligand for PET with picomolar affinity and a high selectivity for D2 and D3 receptors (association constant $K_{a(D2)} = 0.018 \text{ nM}$) (Loc'h et al., 1996), has made possible the comparison of the binding of various antipsychotic compounds to extrastriatal and striatal structures. In order to compare four atypical antipsychotics with a traditional molecule at the recommended dose range for therapeutic antipsychotic effect, we studied the binding of the reference compound haloperidol ($K_{a(D2)} = 1 \text{ nM}$) and that of four atypical antipsychotics – risperidone ($K_{a(D2)} = 3 \text{ nM}$), clozapine ($K_{a(D2)} = 125 \text{ nM}$), amisulpride ($K_{a(D2)} = 3.4 \text{ nM}$ and $K_{a(D2)} = 3.5 \text{nM}$) and olanzapine ($K_{a(D2)} = 11 \text{nM}$) (Chivers et al., 1988) – in patients with schizophrenia treated with these compounds.

METHOD

Subjects

Nineteen patients with DSM-IV (American Psychiatric Association, 1994) schizophrenia (16 males, 3 females, mean age=32 years, s.d.=7) treated with haloperidol (n=4), risperidone (n=3), clozapine (n=3), amisulpride (n=5) or olanzapine (n=4) were included (Table 1). They were treated with daily dosages matching the recommended ranges for antipsychotic effect. For haloperidol this range was 3–20 mg/day (Edtions du Vidal, 1993; Zimbroid et al., 1997); for risperidone, 6–12 mg/day (Kasper, 1998; Nyberg et al., 1999); for clozapine, 200–400 mg/day (Fitron & Heel, 1990); for amisulpride, 200–1200 mg/day (Couchell et al., 1996); and for olanzapine, 5–20 mg/day (Kasper, 1998). Patients were scanned 18–20 h after the last evening dose of the antipsychotic, in order to avoid the peak plasma concentration following the drug dose intake. All patients were medicated for at least 15 days, which is much longer than the five half-lives necessary to reach the steady state for plasma antipsychotic concentration. Exclusion criteria included neurological or other medical conditions and substance misuse. Anticholinergic drugs or benzodiazepines that do not interfere with D2 dopamine receptors (Burt et al., 1976; Boyson et al., 1988) were not withdrawn. The patient groups were compared with a group of six normal control men (mean age=24 years, s.d.=4) who underwent a medical examination and a psychiatric interview in order to rule out any medical condition. The Henri Mondor ethics committee approved the protocol. After a complete description of the study to the subjects, written informed consent was obtained.

Brain imaging

Brain imaging, image analysis and determination of the D2 dopamine blockade by
Table 1  Characteristics of the patients

<table>
<thead>
<tr>
<th>Subject code</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Positive symptom score¹</th>
<th>Negative symptom score¹</th>
<th>Drug</th>
<th>Oral drug dose (mg/day)</th>
<th>Plasma drug concentration (µg/l)</th>
<th>Binding index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>34</td>
<td>F</td>
<td>16</td>
<td>29</td>
<td>Haloperidol</td>
<td>3</td>
<td>6</td>
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</tr>
<tr>
<td>H2</td>
<td>22</td>
<td>M</td>
<td>14</td>
<td>19</td>
<td>Haloperidol</td>
<td>8</td>
<td>8.3</td>
<td>80.6</td>
</tr>
<tr>
<td>H3</td>
<td>42</td>
<td>M</td>
<td>23</td>
<td>24</td>
<td>Haloperidol</td>
<td>15</td>
<td>22</td>
<td>84.7</td>
</tr>
<tr>
<td>H4</td>
<td>29</td>
<td>F</td>
<td>15</td>
<td>21</td>
<td>Haloperidol</td>
<td>60</td>
<td>52</td>
<td>93.2</td>
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<tr>
<td>R1</td>
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<td>M</td>
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<td>15</td>
<td>Risperidone</td>
<td>6</td>
<td>41</td>
<td>67</td>
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<tr>
<td>R2</td>
<td>32</td>
<td>M</td>
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<td>25</td>
<td>Risperidone</td>
<td>8</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
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<td>M</td>
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<td>22</td>
<td>Risperidone</td>
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<td>65.8</td>
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<tr>
<td>C1</td>
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<td>M</td>
<td>24</td>
<td>28</td>
<td>Clozapine</td>
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<td>114</td>
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<td>M</td>
<td>20</td>
<td>23</td>
<td>Clozapine</td>
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<td>262</td>
<td>17.8</td>
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<td>F</td>
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<td>13</td>
<td>Clozapine</td>
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<td>45.9</td>
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<tr>
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</tr>
<tr>
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<td>M</td>
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<tr>
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<td>Amisulpride</td>
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<tr>
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<td>M</td>
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<td>M</td>
<td>24</td>
<td>28</td>
<td>Olanzapine</td>
<td>10</td>
<td>ND</td>
<td>43</td>
</tr>
<tr>
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<td>30</td>
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</tr>
<tr>
<td>O3</td>
<td>25</td>
<td>M</td>
<td>16</td>
<td>23</td>
<td>Olanzapine</td>
<td>20</td>
<td>ND</td>
<td>69.6</td>
</tr>
</tbody>
</table>

ND, not determined.

¹ Positive and Negative Syndrome Scale (PANSS): each score represents the sum of seven items; a score of 7 means an absence of symptoms; the maximum score is 49.

the computation of a binding index were performed according to a methodology described previously (Xiberas et al, 2001). Briefly, for each subject a 1.5 T Signa Imager (General Electric, Milwaukee, WI) provided 128 anatomical slices parallel to the orbito-meatal line. Afterwards, 63 cerebral slices parallel to the orbito-meatal line were acquired with a Siemens HR+ positron tomograph (of spatial resolution 2.5 mm; Knoxville, TX). Just before injecting the [¹⁸F]-FB457, venous blood was sampled for plasma concentration of the antipsychotic drug. Approximately 1 mCi of [¹⁸F]-FB457 was injected into each subject (mean (s.d.)=0.98 (0.20) mCi for healthy subjects and 1.03 (0.23) mCi for patients, Mann–Whitney U=53.5, P=0.82), with a high specific activity of 264±164 µCi/nmol for healthy subjects and 481±299 µCi/nmol for patients (Mann–Whitney U=-29, P=0.08). Afterwards, a first image series was acquired: two 5-min images, two 10-min images and two 15-min images. Then the subjects were removed from the tomograph for 60 min and afterwards placed in the same position using a thermoplastic-modelled mask as well as skin marks with respect to a laser beam system, in order to acquire a late image series: one 30-min and one 15-min image. Finally, a second transmission scan was performed for co-registration purposes.

Image analysis
For each subject, the first PET image series was co-registered on the magnetic resonance image (MRI) using the first transmission scan (Mangin et al, 1994). Because the radioactivity concentrated mainly in the striatum in the late image series, the cortical structures could not be used for registration. Therefore, the second transmission scan was used for PET to MRI co-registration. Regions of interest (ROIs) were drawn on the co-registered MRI slices, following the visible borders of the structures in each hemisphere. Caudate and putamen were defined on five slices, thalamus on four slices and temporal cortices on four slices below the lowest striatum slice; finally, ROIs were defined in the cerebellar grey matter on four slices.

Regional radioactivity concentrations for each region (injected dose- and decay-corrected) were computed by pooling the corresponding ROI values and by summing the left and right regional values.

Determination of D₂ dopamine receptor blockade: binding index computation
Regional radioactivity was measured for each sequential scan and plotted against time. Specific binding in the ROIs was defined as the difference between radioactivities in the ROIs and the cerebellum. The activity measured (A₀) in the ROIs represents the sum of the free (and non-specific binding) and bound radioligand concentrations:

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\[ A_{u0}(\text{ROIs}) = A_{u0}(\text{ROIs}) + C \]

where \( A_{u0} \) is the specifically bound radioactive concentration in the ROIs and \( C \) is the activity measured in the cerebellum, which represents (under the assumption that the concentration of \( D_2 \) dopamine receptors in the cerebellum is negligible with respect to the concentration in the other regions) both free ligand and non-specific binding. This method has been validated in vitro (Altar et al., 1985) and in vivo using PET with previous \( D_2 \) dopamine receptor ligands (Farde et al., 1985), as well as for the \([\alpha^2\text{Br}]-\text{FLB457} \) (Xiberras et al., 2001). Hence, for each patient a binding index (BI) of the antipsychotic compound was derived from the patient's measured regional radioactivity concentrations in the striatum, the extrastriatal regions (thalamus, temporal cortex) and the cerebellum at the time of 165 min, taking the measures of control subjects as a baseline:

\[ \text{BI} (%) = 100 - \frac{\left( \text{regional } A_u - C \right)_{\text{patients}}}{\left( \text{regional } A_u - C \right)_{\text{controls}}} \]

**Plasma drug concentration determination**

**Haloperidol**

After extraction from alkalised plasma by a mixture of hexane/soyamyl alcohol, haloperidol was purified from a Kromasil C8 column (5 µm, 250 × 4.6 mm) using a 73/23 mixture of phosphate buffer (pH 3) and acetonitrile as mobile phase. The wavelength was set at 280 nm. The detection limit was 1.0 µg/l.

**Risperidone**

After extraction from alkalised plasma by a mixture of hexane/ethylacetate, the risperidone was purified from a Kromasil C8 column with the same characteristics as those described for haloperidol.

**Clozapine**

After extraction from alkalised plasma by a mixture of hexane/soyamyl alcohol, the clozapine was purified from a Spherisorp C8 column (5 µm, 250 × 4.6 mm) using a 55/40/5 mixture of phosphate buffer (pH 3), acetonitrile and methanol as mobile phase. The wavelength was set at 230 nm. The detection limit was 2.5 µg/l.

**Amisulpride**

After extraction from alkalised plasma by a mixture of diethyl ether and chloroform, the amisulpride was purified from a µBondapak C18 column (5 µm, 150 × 4.6 mm) using a 90/10 mixture of phosphate buffer (pH 3) and acetonitrile as mobile phase. Detection was performed using a fluorimetric detector set at \( \lambda_{ex} = 280 \text{ nm and } \lambda_{em} = 370 \text{ nm. The detection limit was 0.5 µg/l.} \]

**Olanzapine**

Owing to technical reasons, plasma drug concentration determinations were not available.

**RESULTS**

Individual characteristics of patients and treatments, as well as antipsychotic plasma concentrations and binding index values, are reported in Table 1. Figure 1 shows an example of time-radioactivity curves. Paired comparisons for the binding indices in striatal and extrastriatal regions across treatment groups (Table 2) showed that the striatal and thalamic binding indices graded the haloperidol and atypical antipsychotics (Fig. 2). This was not the case in the temporal cortex.

![Fig. 1](image)  
**Fig. 1** Time-radioactivity curves in the striatum of control subject group and of patients treated with various dosages of haloperidol.

**DISCUSSION**

Patients treated with the usual antipsychotic dose ranges of haloperidol, risperidone, clozapine, amisulpride and olanzapine had a similarly high \( D_2 \) dopamine receptor blockade in the temporal cortex, as estimated by the binding index of \([\alpha^2\text{Br}]-\text{FLB457} \). In contrast, the atypical antipsychotic drugs induced a significantly lower \( D_2 \) binding index than haloperidol in basal ganglia (i.e. in the thalamus and particularly in the striatum).
Table 2  Comparison of binding indices in striatum, thalamus and temporal cortex

<table>
<thead>
<tr>
<th>Intergroup comparisons by Kruskal–Wallis test</th>
<th>Paired-group comparisons (mean (s.d.)) by Mann–Whitney test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol v. risperidone</td>
<td>Haloperidol v. clozapine</td>
</tr>
<tr>
<td>Haloperidol v. amisulpride</td>
<td>Haloperidol v. olanzapine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Striatum</th>
<th>81.5 (11.5) v. 63.3 (5.5)</th>
<th>81.5 (11.5) v. 32.8 (14.2)</th>
<th>81.5 (11.5) v. 41.6 (16.3)</th>
<th>81.5 (11.5) v. 45.1 (20.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0; P = 0.11</td>
<td>0.0; P = 0.05</td>
<td>0.0; P = 0.01</td>
<td>1.0; P = 0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thalamus</th>
<th>94.2 (2.1) v. 89.8 (3.3)</th>
<th>94.2 (2.1) v. 63.0 (14.2)</th>
<th>94.2 (2.1) v. 73.3 (14.8)</th>
<th>94.2 (2.1) v. 64.4 (20.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5; P = 0.11</td>
<td>0.0; P = 0.05</td>
<td>0.0; P = 0.02</td>
<td>1.0; P = 0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temporal cortex</th>
<th>91.7 (4.2) v. 91.6 (3.3)</th>
<th>91.7 (4.2) v. 77.8 (10.7)</th>
<th>91.7 (4.2) v. 80.9 (16.1)</th>
<th>91.7 (4.2) v. 83.6 (10.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U = 6.0; P = 1</td>
<td>U = 2.0; P = 0.23</td>
<td>U = 3.0; P = 0.11</td>
<td>U = 4.5; P = 0.34</td>
</tr>
</tbody>
</table>

Patient’s measured regional radioactivity concentrations in the striatum, the extra-striatal regions (thalamus, temporal cortex) and the cerebellum 165 min after injection (Fig. 1), using the measures in control subjects as a baseline. The time was chosen from modelling studies in primates, because it tallies with the duration required for the radioligand’s equilibrium in the extra-striatal regions (Delforge et al., 1999). However, according to the same model, equilibrium is reached only at t = 300 min after injection in striatal regions. In one control subject, we measured the concentration of the radioactivity in the striatum at 165 and 315 min after injection: an increase of 10% only (139 v. 152 nCi/ml) was observed at 315 min. Thus, the binding in the striatum is probably slightly underestimated and values reported for striatal regions should not be considered as effective D₂ receptor occupancy figures but as approximate values. They are, nevertheless, useful to compare the striatal D₂ receptor blockade induced in vivo by various antipsychotic drugs.

**Picomolar affinity radioligand**

The picomolar affinity of [¹²⁵I]-FLB457 for D₂ receptors accounts for the detection of a decrease of cerebellar radioactivity values in treated patients, which is likely to reflect some degree of occupancy of the small concentration of cerebellar D₂ receptors. This was not detected in previous studies using lower-affinity D₂ radioligands. Although the cerebellar radioactivity cannot be considered as solely reflecting non-specific binding of the [¹²⁵I]-FLB457, in the conditions of the present study the use of a subtractive operator in the binding index computation (i.e. regional A₁ – C) limits the incidence of the cerebellar specific binding for comparison of the binding index under various antipsychotic treatments. Indeed, by using the mean cerebellar value observed in the healthy subjects as a reference, underestimation of binding index values was below 5% in the striatum but ranged from 4% (haloperidol) to 12% (clozapine) in the temporal cortex.

This underestimation, more marked in cortical than in striatal structures, strengthens the observation of a high binding index in cortical regions with all antipsychotics and the differential binding index values between haloperidol and atypical compounds in the basal ganglia. This observation is in keeping with a modelling study, correlating the affinity of a ligand with the Bₘₐₓ in the structure studied. According to that modelling, the apparent affinity of a radioligand is correlated with the Bₘₐₓ in the structure: when the Bₘₐₓ is low, the apparent affinity of the radioligand to its receptor increases (Delforge et al., 1999).

**Consistency with previous ex vivo findings in animals**

The high D₂ blockade induced in the temporal cortex by each of the five antipsychotic drugs is consistent with reports using different methodologies. The topographical selectivity of atypical antipsychotics on dopamine blockade has been reported previously from ex vivo measurements in animals. For instance, studies have demonstrated a higher affinity of amisulpride for D₂ dopamine receptors in the temporal regions than in striatum (Schoemaker et al., 1997). Also, chronic treatment with clozapine has been shown specifically to upregulate cortical D₂ mRNA turnover and cortical D₂ receptor binding, at variance with haloperidol, which seems to upregulate both striatal and cortical D₂ receptors (Lidow & Goldman-Rakic, 1994). Atypical antipsychotics raise dopamine turnover.

**Methodological considerations**

**Long-time-frame PET imaging**

For each patient, a binding index of the antipsychotic drug was derived from the

![Fig 2 Binding indices of haloperidol, risperidone, clozapine, amisulpride and olanzapine in the striatum (a), thalamus (b) and temporal cortex (c).](image-url)
more in limbic structures than in striatum, whereas traditional antipsychotics affect the dopamine turnover in both regions to the same degree (Westerink et al., 1977). In addition, the c-fos-like immunoreactivity is increased by atypical antipsychotics in limbic areas and in cortices, whereas traditional antipsychotics also lead to an increased c-fos expression in the dorsolateral striatum (Fink-Jensen & Kristensen, 1994).

Consistency with previous in vivo findings in humans

Our results obtained with a quantitative imaging technique are in agreement with previous in vivo reports using a radioligand with the same picomolar affinity for D2 receptors ([123I]-epidepride) and single photon emission tomography to assess the ‘occupancy’ of D2 receptors by antipsychotic drugs in the striatum and temporal cortex. Indeed, the elevated occupancy figures observed with traditional compounds (haloperidol, fluphenazine, flupenthixol, pipotiazine, droperidol) in both temporal (mean 82%) and striatal (mean 73%) regions (Biglani et al., 1999), and the small difference between striatal and temporal cortex blockade were analogous to those determined in the haloperidol-treated patients of the present study. Thus, although a relative temporal cortex selectivity in D2 blockade (Pilowsky et al., 1997; Biglani et al., 2000) appears to characterise atypical antipsychotics, a similar high D2 blockade in both temporal and striatal regions is induced by usual antipsychotic doses of traditional antipsychotics.

On the whole, the convergence of ex vivo and in vivo data strongly suggests that cortical D2 dopamine receptors are a common target of both traditional and atypical antipsychotics for therapeutic action.

Finally, from a clinical point of view, our results are in keeping with the association of antipsychotic efficacy (attributed to an action on meso-cortico-limbic dopamine pathways) and lower extrapyramidal side-effects (attributed to an antipodalaminergic activity in the dorsolateral striatum) with atypical antipsychotics than with traditional compounds. Searching for a high in vivo binding to the D2 receptors in the cortex co-occurring with a lower binding in the basal ganglia therefore could be suggested as an indicator of a favourable benefit/risk profile for a putative antipsychotic compound.

CLINICAL IMPLICATIONS

- Cortical D2 dopamine receptors are a common target of both traditional and atypical antipsychotics for therapeutic action.
- In the basal ganglia, atypical antipsychotics antagonise the dopamine transmission mediated by the D2 receptor to a lower level than traditional antipsychotics.
- The co-occurrence of a high in vivo binding to the D2 receptors in the cortex and a lower binding in the basal ganglia could be an indicator of a favourable benefit/risk profile for a putative antipsychotic compound.

LIMITATIONS

- Owing to the small patient samples, inter-individual variability was not assessed extensively.
- The binding indices approximate the effective D2 receptor occupancy.
- The study was not designed to assess therapeutic effects longitudinally.

ACKNOWLEDGEMENTS

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