## CHAPTER 3

# IN VIVO QUANTIFICATION OF STRIATAL DOPAMINE $D_2$ RECEPTOR OCCUPANCY BY JNJ-37822681 USING [$^{11}$C]RACLOPRIDE AND POSITRON EMISSION TOMOGRAPHY

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## ABSTRACT

JNJ-37822681 is a novel, fast-dissociating dopamine $D_2$ receptor antagonist, currently in development as an antipsychotic drug candidate. A previous first-in-human study demonstrated mild central nervous system effects of JNJ-37822681 in healthy male volunteers. Significant but transient serum prolactin elevations were demonstrated, whereas other neurophysiological effects were relatively small. To investigate striatal dopamine $D_2$ receptor occupancy by variable single doses of JNJ-37822681, an open-label [$^{11}$C]raclopride positron emission tomography study was performed in twelve healthy male volunteers, using the simplified reference tissue model with cerebellum as reference tissue. Oral administration of JNJ-37822681 resulted in dose-dependent dopamine $D_2$ receptor occupancy. Receptor occupancy increased from 9-19% at 2 mg doses to 60-74% at 20 mg doses of JNJ-37822681. Therefore, single oral doses of JNJ-37822681 can produce occupancy levels that are generally associated with clinical efficacy for registered antipsychotic drugs.

## INTRODUCTION

The theory that rapid dissociation rates of an antipsychotic drug from the dopamine $D_2$ receptor is a principal pharmacological characteristic that determines the distinct effect profile of atypical antipsychotic drugs, has been proposed specifically to explain the lower incidence of extrapyramidal side effects, hyperprolactinaemia or secondary negative signs compared with typical antipsychotic drugs[1–6]. However, this theory may not fully explain the efficacy of clozapine in treatment-resistant schizophrenia[7,8]. In addition, it has been argued that this hypothesis does not apply to all atypical antipsychotic drugs but only to drugs such as clozapine and quetiapine, which have low affinity for the dopamine $D_2$ receptor[7,9–11]. Nevertheless, despite the limitations of the 'fast dissociation hypothesis' as a general model for atypical drug action, screening of novel compounds by their respective dissociation rates may be a useful means to select novel antipsychotic drug candidates with an improved side effect profile. Moreover, development of a novel compound with selectivity for the dopamine $D_2$ receptor and a fast rate of dissociation can provide an opportunity to study the 'fast dissociation hypothesis' in a prospective clinical setting.

Recently, the novel chemical entity JNJ-37822681 was developed, which combines selectivity for the dopamine $D_2$ receptor with a fast rate of dissociation[12]. JNJ-37822681 has moderate affinity for the dopamine $D_{2L}$ receptor and low affinity for dopamine $D_1$ and $D_3$ receptors, serotonin 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors, histamine $H_1$ receptors and adrenergic $\alpha_{1A}$ receptors[12]. JNJ-37822681 also binds to the $\sigma_1$ receptor. When tested in parallel, the time for 50% dissociation of [$^3$H]JNJ-37822681 from the dopamine $D_{2L}$ receptor was similar to that of [$^3$H]clozapine and significantly faster than that of [$^3$H]haloperidol, [$^3$H]risperidone and [$^3$H]paliperidone[12]. In animal models, JNJ-37822681 antagonized apomorphine-induced behavior in rats with a low potential for catalepsy[12]. In a separate study, pharmacokinetics and central nervous system (CNS) effects of JNJ-37822681 were evaluated in healthy volunteers[13]. The main pharmacodynamic effect was a dose-related elevation of serum prolactin starting at doses of 5 mg, whereas other subjective and neurophysiological effects were small and only observed at higher doses. Somnolence was the most frequent reported adverse event. No significant extrapyramidal effects were noted, although transient mild restlessness (akathisia) was reported occasionally after higher doses. The purpose of the present study was to characterize the relationship between plasma concentration following single oral doses of JNJ-37822681 and striatal dopamine $D_2$ receptor occupancy in vivo.

## METHODS

### *Study design*

An open-label study was performed to obtain 16 positron emission tomography (PET) scans using [$^{11}$C]raclopride, after administration of various dosages of JNJ-37822681 in healthy male volunteers, in order to characterize the saturation curve of JNJ-37822681 within tolerable dose levels. To enable calculation of dopamine $D_2$ receptor occupancy, baseline PET scans without prior administration of JNJ-37822681 were also performed in each volunteer. The study was approved by the medical ethics review committee of the VU University Medical Center in Amsterdam. Prior to medical screening, all volunteers gave written informed consent. Medical screening included medical history, physical examination, urinalysis, routine haematology and chemistry, 12-lead electrocardiography and an MRI scan to exclude cerebral pathology. Up to three [$^{11}$C]raclopride PET scans were performed per individual volunteer: one baseline scan and up to two scans following a single oral dose of JNJ-37822681. The postdose scans were initiated 2 hours (±30 minutes) after dosing. This time point was chosen to coincide with the expected $t_{max}$ of the plasma concentrations of JNJ-37822681 (which varied between approximately 4 hours after 0.5 mg to 1.5 hours after 20 mg) and the presence of central nervous system effects (which were maximal between 1 and 3 hours after dosing)[13]. The first two volunteers were scanned following administration of 10 mg of JNJ-37822681. This 10 mg dose was expected to result in a dopamine $D_2$ receptor occupancy of about 75%, based on previous PET studies of JNJ-37822681 in Cynomolgus monkeys and pharmacokinetic data from healthy volunteers[13]. Subsequent doses were chosen based on the outcomes of the previous PET scans. The maximum dose was set to 20 mg JNJ-37822681, because safety data above 20 mg were not available at the time of study execution. Moreover, preclinical studies suggested that this dose would result in significant occupancy of striatal dopamine $D_2$ receptors and allow for reasonable estimation of the dose-occupancy relationship. Blood samples for pharmacokinetic analyses of JNJ-37822681 were taken before dosing and prior to, at the midpoint of and immediately after each scan. Plasma concentrations of JNJ-37822681 were determined using liquid chromatography-mass spectrometry. At several time points, development of akathisia or other extrapyramidal symptoms was evaluated using the Barnes akathisia rating scale and the Simpson-Angus scale[14,15]. In addition, blood pressure and heart rate measurements, 12-lead electrocardiograms, urinalysis, alcohol breath test and routine blood chemistry and haematology were performed on the days before and after administration of JNJ-37822681. Administration of first and second doses of JNJ-37822681 was always separated by a washout time of at least 7 days.

### *Magnetic resonance imaging (MRI)*

T1-weighted gradient echo pulse MRI scans were obtained using a Philips 3 Tesla Achieva scanner (Philips Healthcare Nederland, Eindhoven, The Netherlands). These scans were used to exclude cerebral pathology and to define regions of interest (ROI).

### *Positron emission tomography (PET)*

PET scans were performed on an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, Tennessee, USA), equipped with a neuro-insert to reduce the contribution of scattered photons. This scanner enables the acquisition of 63 transaxial planes over a 15.5 cm axial field of view[16]. First, using three retractable rotating line sources, a 10 minute transmission scan was performed in 2D acquisition mode. This scan was used to correct the subsequent emission scan for photon attenuation. Next, a dynamic emission scan in 3D acquisition mode was performed. Data acquisition comprised of 21 frames ($6 \times 5$, $3 \times 10$, $4 \times 60$, $2 \times 150$, $2 \times 300$ and $4 \times 600$ seconds) with a total duration of 60 minutes. At the start of this scan, 196 ± 13 MBq [$^{11}$C]raclopride with specific activity (SA) in the range of 32-111 GBq/μmol and a total volume of 12 mL was administered intravenously using an infusion pump (MEDRAD, Beek, The Netherlands) at a rate of 0.8 mL/sec, followed by a flush of 42 mL saline at 2.0 mL/sec. The total injected amount of raclopride did not differ significantly between baseline and postdose PET scans (1.33 ± 0.52 μg and 1.09 ± 0.98 μg respectively, $p = 0.38$) and all amounts were less than 1% of a clinically active raclopride dose (range 0.48-4.43 μg). The scanning protocol was identical for baseline and postdose scans. [$^{11}$C]raclopride was produced in the government licensed GMP facility of the department of Nuclear Medicine & PET Research (no. 108897F) according to current GMP guidelines (EudraLex volume 4) using a previously reported method[17].

### *Image analysis*

All PET sinograms were corrected for dead time, scatter, decay, randoms and tissue attenuation and reconstructed using filtered back projection with a 0.5 Hanning filter, resulting in a transaxial spatial resolution of ~ 7 mm full width at half maximum in the centre of the field of view. Images were then transferred to ULTRASPARC workstations (Sun Microsystems Inc., Santa Clara, California, USA) for further analysis. For each subject, all scans were co-registered to the corresponding individual MRI. Left and right putamen, together with cerebellum, ROI were defined manually on the MRI scan and then projected onto the co-registered PET scans, guaranteeing identical ROI for all successive scans of the same subject. Total putamen was obtained as the volume weighted average of

left and right putamen. Putamen time-activity curves were analysed using the simplified reference tissue model (SRTM) with cerebellum as reference tissue[18]. This provides an estimate of the nondisplaceable binding potential $BP_{ND}$[19]. For each [$^{11}$C]raclopride scan following administration of JNJ-37822681, dopamine $D_2$ receptor occupancy in putamen was derived by relating its $BP_{ND}$ ($BP_{ND}^{drug}$) to the corresponding baseline $BP_{ND}$ ($BP_{ND}^{baseline}$):

$$\text{Receptor occupancy}\,(\%) = \left[1 - \frac{BP_{ND}^{drug}}{BP_{ND}^{baseline}}\right] \times 100\,\%$$

This approach assumes that affinity is not affected by a pharmacological dose of JNJ-37822681. For illustrative purposes, the simplified reference tissue model was also applied at the voxel level using a basis function implementation of SRTM, generating parametric images of $BP_{ND}$[20]. To describe the induced $D_2$ receptor occupancy as a function of plasma concentration of JNJ-37822681, data were fitted to the following equation:

$$\text{Receptor occupancy}\,(\%) = \frac{100 \times C_P}{C_P + EC_{50}}$$

where $C_p$ stands for the plasma concentration of JNJ-37822681 and $EC_{50}$ for the estimated plasma concentration of JNJ-37822681 that results in 50% receptor occupancy. $C_p$ was calculated as the mean of plasma concentrations of JNJ-37822681, measured prior to, at midpoint of and immediately after each PET scan.

Data were further analyzed using PVE-lab, a software program using a probability map of 35 delineated ROI that has been validated previously[21], in order to evaluate receptor occupancy in the caudate nucleus, putamen and striatum (left, right and total).

## RESULTS

### *Subjects*

All participants were healthy males, aged 18 to 34 years, with a body mass index ranging from 20 to 29 kg/m$^2$. Four included volunteers dropped out before administration of JNJ-37822681 and their first planned postdose PET scan for reasons unrelated to the study. Data obtained in these volunteers were not used for analysis. Four volunteers completed one baseline [$^{11}$C]raclopride scan and two scans following administration of different doses of JNJ-37822681. Eight additional volunteers underwent one baseline and only one postdose scan. Therefore, in total, data were obtained in 12 volunteers, consisting of 12 baseline scans and 16 postdose scans with six different doses of JNJ-37822681 ranging from 2 to 20 mg.

### *Clinical observations*

All reported adverse events were mild in severity. The most commonly reported adverse event was somnolence, occurring three times after 15 mg and three times after 20 mg of JNJ-37822681. A mild restless feeling after administration of 20 mg was reported by one volunteer. There were no consistent and clinically relevant abnormalities in blood pressure, heart rate, 12-lead electrocardiogram, blood chemistry and haematology. In addition, no consistent and clinically relevant changes were observed on the Barnes akathisia rating scale and the Simpson-Angus scale.

### *Plasma concentration of JNJ-37822681*

Plasma concentrations of JNJ-37822681, measured prior to, at midpoint of and immediately after each PET scan, are shown in Table 1.

**TABLE 1** Plasma concentration of JNJ-37822681 in all individual subjects. The mean plasma concentration of JNJ-37822681 was determined from plasma samples taken immediately before, at midpoint, and immediately after PET scanning.

| Dose (mg) | Subject number | Plasma JNJ-37822681 (ng/mL) | | | |
|---|---|---|---|---|---|
| | | Prior to PET scan | At midpoint of PET scan | After PET scan | Mean |
| 2 | 1006 | 1.92 | 1.63 | 1.59 | 1.71 |
| 2 | 1102 | 1.41 | 1.71 | 2.93 | 2.02 |
| 2 | 1105 | 1.96 | 1.84 | 1.65 | 1.82 |
| 5 | 1002 | 10.9 | 7.34 | 6.06 | 8.10 |
| 5 | 1007 | 8.05 | 5.92 | 5.29 | 6.42 |
| 7 | 1107 | 11.9 | 8.82 | 11.2 | 10.6 |
| 10 | 1001 | 19.4 | 16.8 | 15.0 | 17.1 |
| 10 | 1002 | 19.8 | 14.0 | 11.6 | 15.1 |
| 15 | 1003 | 25.8 | 20.6 | 22.3 | 22.9 |
| 15 | 1005 | 32.5 | 27.1 | 21.7 | 27.1 |
| 15 | 1106 | 33.1 | 18.8 | 16.4 | 22.8 |
| 20 | 1003 | 10.6 | 13.1 | 17.6 | 13.8 |
| 20 | 1004 | 49.5 | 37.9 | 36.4 | 41.3 |
| 20 | 1005 | 74.5 | 52.7 | 39.2 | 55.5 |
| 20 | 1007 | 30.7 | 24.0 | 20.5 | 25.1 |
| 20 | 1101 | 57.7 | 49.8 | 42.6 | 50.0 |

### *Binding potential and $D_2$ receptor occupancy*

$BP_{ND}$ values and $D_2$ receptor occupancies in the manually defined left and right putamen are shown in Table 2. Average baseline $BP_{ND}$ was 2.85 ± 0.21 (range 2.38 to 3.06). A decrease in $BP_{ND}$ and corresponding increase in receptor occupancy was seen with increasing doses of JNJ-37822681. Examples of reconstructed parametric $BP_{ND}$ images are shown in Figure 1. Receptor occupancy increased from 9-19% after an oral dose of 2 mg to 60-74% after an oral dose of 20 mg of JNJ-37822681, as illustrated in Figure 2. Receptor occupancy as a function of plasma concentration of JNJ-37822681 provided an estimated $EC_{50}$ of 14.5 ng/mL (coefficient of variation 5.4%). The associated hyperbolic function is shown in Figure 3.

Calculated $D_2$ receptor occupancies in the caudate nucleus, putamen and striatum using PVE-lab, are shown in Table 3. In general, occupancy levels by JNJ-37822681 in caudate nucleus and putamen were similar.

**FIGURE 1** Transaxial (left), coronal (middle) and sagittal (right) parametric $BP_{ND}$ images of subject 1007, co-registered to corresponding MRI data. Top row represents baseline images, obtained prior to administration of medication. Middle row represents images following administration of 5 mg of JNJ-37822681, resulting in striatal $D_2$ receptor occupancy of 30%. Bottom row represents images following administration of 20 mg of JNJ-37822681, resulting in striatal $D_2$ receptor occupancy of 65%.

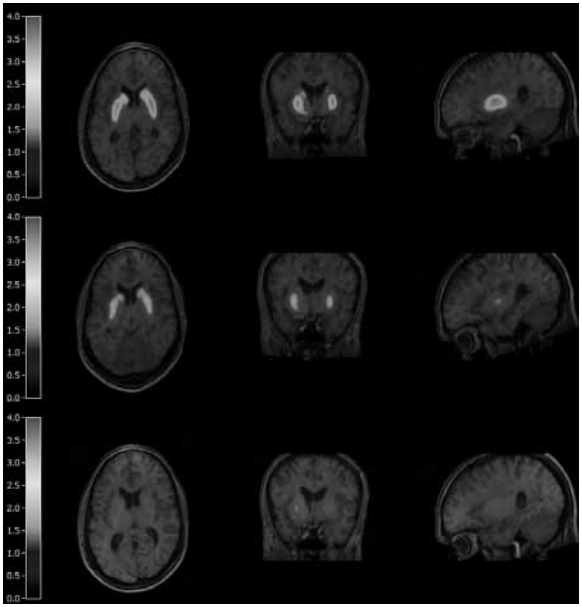

**FIGURE 2** Dopamine $D_2$ receptor occupancy as function of administered dose of JNJ-37822681 for manually defined putamen (volume weighted average of left and right putamen).

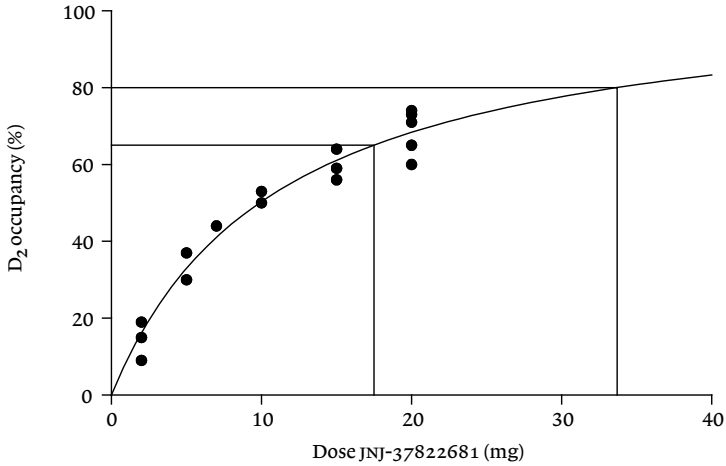


**FIGURE 3** Dopamine $D_2$ receptor occupancy as function of mean plasma concentration of JNJ-37822681 for manually defined putamen (volume weighted average of left and right putamen). The fitted curve indicates that receptor occupancy between 65 and 80% is achieved by plasma concentrations between 27 and 58 ng/mL.

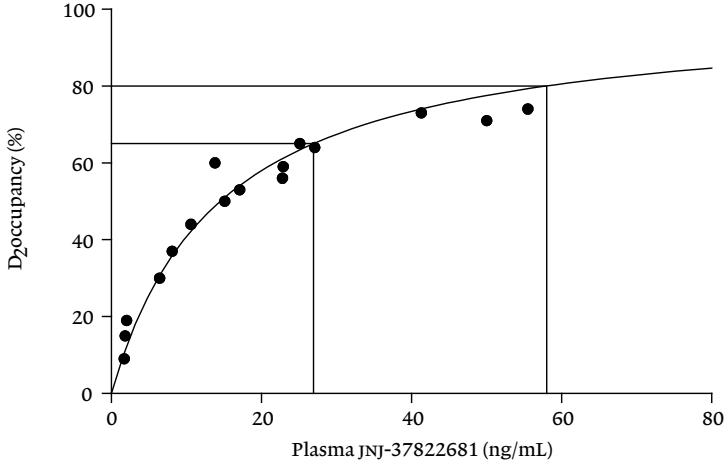

**TABLE 2** Binding potential ($BP_{ND}$) and dopamine $D_2$ receptor occupancy levels in all subjects for manually defined putamen (volume weighted average of left and right putamen).

| Dose (mg) | Subject number | Baseline $BP_{ND}$ | Postdose $BP_{ND}$ | $D_2$ receptor occupancy (%) |
|---|---|---|---|---|
| 2 | 1006 | 2.38 | 2.17 | 9 |
| 2 | 1102 | 3.06 | 2.48 | 19 |
| 2 | 1105 | 3.01 | 2.56 | 15 |
| 5 | 1002 | 3.01 | 1.90 | 37 |
| 5 | 1007 | 2.69 | 1.87 | 30 |
| 7 | 1107 | 2.85 | 1.61 | 44 |
| 10 | 1001 | 3.01 | 1.41 | 53 |
| 10 | 1002 | 3.01 | 1.52 | 50 |
| 15 | 1003 | 2.90 | 1.20 | 59 |
| 15 | 1005 | 3.06 | 1.09 | 64 |
| 15 | 1106 | 2.74 | 1.21 | 56 |
| 20 | 1003 | 2.90 | 1.15 | 60 |
| 20 | 1004 | 2.80 | 0.77 | 73 |
| 20 | 1005 | 3.06 | 0.78 | 74 |
| 20 | 1007 | 2.69 | 0.93 | 65 |
| 20 | 1101 | 2.64 | 0.76 | 71 |

**TABLE 3** Dopamine $D_2$ receptor occupancy in all subjects for PVE-lab defined caudate nucleus, putamen and striatum (left and right).

| Dose (mg) | Subject number | Caudate nucleus | Putamen | Whole striatum |
|---|---|---|---|---|
| 2 | 1006 | 13,6 | 11,9 | 12,8 |
| 2 | 1102 | 12,1 | 15,5 | 14,3 |
| 2 | 1105 | 22,3 | 19,3 | 20,2 |
| 5 | 1002 | 32,5 | 34,1 | 33,2 |
| 5 | 1007 | 41,3 | 29,9 | 34,3 |
| 7 | 1107 | 47,6 | 44,3 | 45,5 |
| 10 | 1001 | 57,5 | 48,7 | 51,8 |
| 10 | 1002 | 50,0 | 49,3 | 49,5 |
| 15 | 1003 | 60,8 | 59,2 | 59,7 |
| 15 | 1005 | 63,4 | 63,5 | 63,4 |
| 15 | 1106 | 62,1 | 55,9 | 57,7 |
| 20 | 1003 | 62,3 | 59,0 | 60,2 |
| 20 | 1004 | 76,8 | 74,5 | 75,4 |
| 20 | 1005 | 75,8 | 73,5 | 74,4 |
| 20 | 1007 | 73,3 | 65,2 | 67,9 |
| 20 | 1101 | 71,4 | 70,7 | 71,1 |

## DISCUSSION

The present study was performed to characterize striatal dopamine $D_2$ receptor occupancy over a range of oral dosages of JNJ-37822681. Dosages from 2 to 20 mg resulted in receptor occupancy levels ranging from 9 to 74%, with a hyperbolic function providing a good description of the saturation curve (see Figure 3).

PET studies following single dose administration of novel compounds in healthy volunteers are widely used in early phase drug development to evaluate binding characteristics in vivo and to guide dose selection for future clinical trials. However, the predictive value of single dose PET studies for dose selection in clinical trials is somewhat limited because single dose estimates may differ from steady state estimates after multiple dosing. For example, single dose PET studies with ziprasidone[22,23] have predicted higher dopamine $D_2$ receptor occupancy than multiple dose studies[23,24]. On the other hand, PET studies in healthy volunteers after single doses of olanzapine[25] and risperidone[26], even in spite of very small sample sizes and limited dose ranges, have provided rather accurate predictions of receptor occupancy in schizophrenic patients following subchronic treatment[27-31]. Preliminary results of a separate PET study with JNJ-37822681 demonstrate that, although refinement after multiple dose administration enhances predictive value to some extent, measurements of $D_2$ receptor occupancy following single doses appear to provide reasonable estimates for guidance and interpretation of clinical studies[32,33].

Several PET studies using [$^{11}$C]raclopride have consistently demonstrated that, following haloperidol treatment, a striatal dopamine $D_2$ receptor occupancy higher than 65% is associated with clinical response, whereas occupancy above 80% is associated with extrapyramidal side effects[34-39]. Similar occupancy levels have been found with other typical agents such as chlorpromazine[40], perphenazine[40] and loxapine[41] and with atypical agents such as risperidone[29-31] and olanzapine[28,29,42]. Accordingly, it has been suggested that 65-80% receptor occupancy is optimal for most registered antipsychotic agents in terms of antipsychotic effect and adverse (i.e. extrapyramidal) events in clinical practice[37,39,43]. The present data indicate that 65 to 80% receptor occupancy is associated with plasma concentrations of 27 to 58 ng/mL of JNJ-37822681 (see Figure 3). However, target levels of 65 to 80% striatal dopamine $D_2$ receptor occupancy do not always represent absolute thresholds for antipsychotic activity and exceptions have been identified. First, PET studies with long-acting depot injections of haloperidol decanoate[44] and risperidone[45] in schizophrenic patients have demonstrated dopamine $D_2$ receptor occupancy levels below 60% without clinical relapse, suggesting that sustained dopamine $D_2$ receptor occupancy be-

tween 65 and 80% (although associated with acute clinical response) may not be necessary to maintain clinical effect. It is possible that lower levels of dopamine $D_2$ receptor occupancy offer some protection against psychotic relapses, or that long-term adaptive changes contribute to the stable clinical situation in chronically well-treated schizophrenic patients. Second, the partial $D_2$ receptor agonist aripiprazole is associated with occupancy levels over 80% at therapeutic doses, while the risk for extrapyramidal symptoms seems to increase only at occupancy levels of 90% or higher[46,47]. This apparent discrepancy with dopamine $D_2$ receptor antagonists, however, could reflect the distinct pharmacological characteristics of aripiprazole. Third, PET studies have demonstrated lower occupancy levels with clozapine[29,35,40] and quetiapine[48] at clinically effective doses. It has been suggested that the occupancy levels of clozapine and quetiapine may have been underestimated because these drugs, compared with other antipsychotics, can rather easily be displaced from the $D_2$ receptor by endogenous dopamine release[5]. Further studies with shorter time intervals between dosing of quetiapine and PET scanning showed higher occupancy levels, reflecting a rapid reduction in occupancy after transiently high levels[49,50].

Despite a fast $k_{off}$, JNJ-37822681 is able to achieve relatively high dopamine $D_2$ receptor occupancy levels. If fast dissociation is the reason why clozapine and quetiapine are therapeutically active at relatively low striatal occupancy levels, this could also be the case for JNJ-37822681. Preliminary results of a recently completed multicenter, double blind, placebo-controlled trial with twice daily dosing of 10, 20 and 30 mg of JNJ-37822681 in patients with schizophrenia indicate clinical efficacy superior to placebo with low frequency of extrapyramidal symptoms with all three dosing regimes[51]. The present study demonstrates that doses of 10 mg of JNJ-37822681 are associated with merely 50-53% receptor occupancy two hours after dose administration. It would be of interest to further study the time course of $D_2$ receptor occupancy, in order to assess whether JNJ-37822681, similar to quetiapine, produces only transiently high levels of receptor occupancy with a rapid reduction over time.

Central neurophysiological and neuropsychological effects of single doses up to 20 mg of JNJ-37822681 are generally quite small with the exception of increases in serum prolactin[13]. Small decreases in adaptive tracking were observed after doses of 10 mg, whereas small reductions in saccadic peak velocity, smooth pursuit eye movements, alertness, finger tapping and $\alpha$ and $\beta$ activity on the EEG and an increase in body sway were observed at higher doses. The present data demonstrate that 20 mg doses of JNJ-37822681 can induce receptor occupancy levels that are generally associated with clinical response (i.e. 65 to 80%) for registered antipsychotic drugs. Therefore, the mild CNS effects of

JNJ-37822681, compared with the increase in serum prolactin, do not seem to result from lack of $D_2$ receptor occupancy. A more likely explanation of these findings may be the selectivity of JNJ-37822681 for the dopamine $D_2$ receptor. Prolactin release is controlled primarily by dopamine acting on dopamine $D_2$ receptors, whereas the other pharmacodynamic tests measure more complex CNS functions, which are likely to involve multiple neurotransmitter receptor systems. Accordingly, specific dopamine $D_2$ antagonism by JNJ-37822681 significantly increases prolactin release, while only moderately affecting the other pharmacodynamic tests.

Within the present small group of healthy volunteers, none of the investigated dosages of JNJ-37822681 was associated with receptor occupancy levels above 80%. Accordingly, akathisia and other extrapyramidal side effects were absent. However, in a previous study with similar doses in healthy volunteers, transient mild restlessness was reported occasionally following the highest dosages[13]. Especially at the higher doses, peak plasma concentrations are reached somewhat earlier than two hours after dosing[13]. Striatal dopamine $D_2$ receptor occupancy could therefore have increased transiently above 80%, with an associated higher risk for peak dose-related extrapyramidal symptoms. To further characterize the relationship between dopamine $D_2$ receptor occupancy by JNJ-37822681 and the emergence of extrapyramidal side effects, PET studies at higher dosages of JNJ-37822681 would be needed. The present study was limited to a maximum dose level of 20 mg JNJ-37822681, because no safety data above 20 mg were available at the time of study execution.

Several imaging studies have demonstrated a non-uniform blockade of striatal $D_2/D_3$ receptors, with higher occupancy levels in the head of the caudate nucleus than in the putamen, by amisulpride[52], risperidone[52], clozapine[53] and aripiprazole[46], although this finding was not replicated for risperidone[54]. To explore this issue, PVE-lab[21] was used in the present study to evaluate occupancy levels by JNJ-37822681 in caudate nucleus and putamen. No clear differences in occupancy levels were found, but sample sizes in the different dosing groups may have been too small.

Postulated clinical importance of dopamine $D_2$ receptor antagonism in extrastriatal limbic and neocortical regions has been a matter of some controversy. Preferential extrastriatal dopamine $D_2$ receptor binding was first demonstrated with clozapine[55] and later with olanzapine[56] using single photon emission computed tomography (SPECT) and [$^{123}$I]epidepride, although PET studies with [$^{11}$C]raclopride and [$^{11}$C]FLB457 did not confirm preferential extrastriatal binding by clozapine[57,58]. However, all these studies have been criticized on methodological grounds[59–61]. Subsequently, other PET studies using [$^{76}$Br]FLB457 or

[$^{18}$F]fallypride have demonstrated preferential extrastriatal binding by clozapine[53,62,63], quetiapine[62,64] and ziprasidone[23], but not haloperidol[63,65]. Contradictory results have been obtained with risperidone and olanzapine, as SPECT using [$^{123}$I]epidepride and PET using [$^{76}$Br]FLB457 demonstrated preferential extrastriatal binding[63,66], whereas PET using [$^{18}$F]fallypride or [$^{11}$C]FLB457 and [$^{11}$C]raclopride in the same subjects, did not[54,65,67]. A recent meta-analysis of SPECT and PET in vivo receptor imaging data[68] demonstrated that both typical and atypical antipsychotic drugs produce high $D_2$ receptor occupancy in temporal cortex, whereas only the typical antipsychotic drugs produced high $D_2$ receptor occupancy in the striatum. The present study using [$^{11}$C]raclopride does not allow for accurate estimation of limbic and neocortical binding characteristics of JNJ-37822681. Future PET studies with high affinity ligands, such as [$^{11}$C]FLB457 and [$^{18}$F]fallypride, are needed to quantify extrastriatal binding by JNJ-37822681. Such studies would also enable evaluation of pituitary dopamine $D_2$ receptor occupancy, as demonstrated in recent PET studies[69,70].

In conclusion, the present results provide guidance for dose selection in future clinical trials using JNJ-37822681 in patients with an acute exacerbation of schizophrenia. Preliminary results of the recently completed multicenter, double blind, placebo-controlled trial with JNJ-37822681 in patients with schizophrenia indicate clinical efficacy superior to placebo with low frequency of extrapyramidal symptoms[51]. Confirmation of these findings may support the usefulness of dissociation rates as a strategy for novel antipsychotic drug development.

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