Striatal $D_{2/3}$ Binding Potential Values in Drug-Naïve First-Episode Schizophrenia Patients Correlate With Treatment Outcome

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One of best validated findings in schizophrenia research is the association between blockade of dopamine D_2 receptors and the effects of antipsychotics on positive psychotic symptoms. The aim of the present study was to examine correlations between baseline striatal $D_{2/3}$ receptor binding potential (BP_p) values and treatment outcome in a cohort of antipsychotic-naïve first-episode schizophrenia patients. Additionally, we wished to investigate associations between striatal dopamine $D_{2/3}$ receptor blockade and alterations of negative symptoms as well as functioning and subjective well-being. Twenty-eight antipsychotic-naïve schizophrenia patients and 26 controls were included in the study. Single-photon emission computed tomography (SPECT) with [123I]iodobenzamide ([123I]-IBZM) was used to examine striatal $D_{2/3}$ receptor BP_p. Patients were examined before and after 6 weeks of treatment with the $D_{2/3}$ receptor antagonist amisulpride. There was a significant negative correlation between striatal $D_{2/3}$ receptor BP_p at baseline and improvement of positive symptoms in the total group of patients. Comparing patients responding to treatment to nonresponders further showed significantly lower baseline BP_p in the responders. At follow-up, the patients demonstrated a negative correlation between the blockade and functioning, whereas no associations between blockade and negative symptoms or subjective well-being were observed. The results show an association between striatal BP_p of dopamine $D_{2/3}$ receptors in antipsychotic-naïve first-episode patients with schizophrenia and treatment response. Patients with a low BP_p have a better treatment response than patients with a high BP_p. The results further suggest that functioning may decline at high levels of dopamine receptor blockade.

Key words: [123I]iodobenzamide/SPECT/occupancy/ amisulpride/subjective well-being

Introduction

Schizophrenia is a complex brain disorder with multifactorial disease mechanisms. In spite of great advances in the understanding of the pathophysiological mechanisms during the last decades, progress in treatment strategies has been hindered by eg, the complexity of the illness and the absence of biologically valid diagnostic criteria.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) data generally support an increase in striatal dopamine release and synthesis capacity in psychotic schizophrenia patients as well as in patients at ultra-high risk for psychosis.[1–12] In recent studies, this is found more pronounced in the associative striatum.[8–10,12] Antipsychotic compounds suppress dopamine activity via blockade of striatal D_2 receptors, and the correlation between antipsychotic potency of first generation antipsychotics (FGAs) in vitro and blockade of the D_2 receptor is well validated.[13,14] In line with this, in vivo studies have found that 60%–70% occupancy of striatal D_2 receptors is required to achieve an antipsychotic effect of FGAs.[15–17]

Most studies of unmedicated schizophrenia patients have failed to demonstrate significant differences of

striatal D_2 receptor BP in patients compared to healthy controls (HC) (for references and review, see Laruelle[18] and Howes et al[19]). The meta-analysis by Laruelle[18] did show a modest (around 12%) elevation in baseline striatal D_2 receptor BP in patients. In a newer meta-analysis, though, no difference between patients and controls was observed, when analyses included only drug-naïve patients.[19] In line with this, 2 studies on unmedicated patients failed to find differences in baseline D_2 receptor BP in patients compared to control.[9,20] However, patients showed a greater change in D_2 BP following pharmacological dopamine depletion than controls, indicating that baseline extracellular dopamine concentrations and D_2 receptor occupancy by dopamine are elevated in schizophrenia. The interpretation of PET and SPECT data on D_2 receptor BP in schizophrenia patients is complicated by the fact that increases in endogenous dopamine release and synthesis are likely to decrease D_2 receptor BP both by direct competition with the ligand and via agonist-induced internalization of the receptors.[21–23] Consequently, the literature tends to support increased dopamine stimulation and decreased availability of striatal D_2 receptors in psychotic patients.

In daily clinical practice, the response of individual patients to antipsychotic treatment differs considerably,[24–28] possibly due to differences in endogenous dopamine activity between patients.[29] In a recent study dopamine synthesis capacity was found to be significantly higher in 12 good responders compared to 12 patients with treatment resistant illness.[11] This may suggest that patients with greater dopamine elevation may be more likely to respond to dopamine blockade. Earlier data from the same group suggest that responders and non-responders represent separate subtypes that may benefit from different treatment approaches.[30] This is consistent with findings from our group, implying subtypes with either serotonergic or dopaminergic disturbances.[31,32] Moreover, growing evidence has shown that glutamatergic disturbances might play a role in schizophrenia, particularly in treatment-resistant patients.[33,34]

In line with the subdivision of schizophrenia patients based on baseline dopamine activity is the finding that some patients have a poor treatment response despite high striatal D_2 receptor occupancy.[35,36] Other data suggest that lower baseline dopamine activity is associated with an increased risk of developing dysphoria, akathisia and extrapyramidal side effects (EPS).[37] In addition to EPS, dopamine receptor occupancy by antipsychotics has also been associated with (secondary) negative symptoms such as avolition, apathy, and affective flattening[38–40] and with subjective experience.[41,42] The Subjective Well-Being under Neuroleptics Scale (SWN)[43] has been used in studies relating subjective experiences with dopaminergic changes. Two studies[44,45] have found a negative association between striatal D_2 receptor occupancy and subjective well-being in patients treated with D_2 antagonists,

and de Haan et al[44] suggest that negative subjective experience might be more sensitive to D_2 receptor occupancy than EPS. Both studies, however, included previously medicated patients.

In general, the literature emphasizes the need for predictive markers for treatment response as well as for development of side effects, thereby sparing patients unnecessary treatment trials and adverse effects. In the search for such markers, it is critical to examine the patients before their brains have been modified by antipsychotic medication and repeated relapses—and to follow the patients over time to study the effects of specific interventions.

In the present study, SPECT $[^{123}I]$-IBZM was used to examine the relationship between baseline $D_{2/3}$ receptor binding potential (BP_p) and treatment outcome in a quite large cohort of antipsychotic-naïve first-episode schizophrenia patients. Additionally, we related $D_{2/3}$ receptor occupancy following 6 weeks of monotherapy with the relatively selective $D_{2/3}$ antagonist amisulpride to functioning and subjective well-being. High resolution PET studies have found dopamine activity more pronounced in the functionally defined associative striatum.[8,9] We used an automatic application of regions dividing the striatum into its anatomic subdivisions; ie, the caudate and the putamen. Since the caudate is part of the associative striatum[46] we used this region as our region of interest. With the spatial resolution of our SPECT system (7.4 mm) we assumed similar to Stone et al[47] that this is sufficient to resolve the caudate from the putamen.

We hypothesized: (1) first-episode schizophrenia patients with low striatal dopamine $D_{2/3}$ receptor BP_p in the antipsychotic-naïve state achieve a better treatment response from striatal $D_{2/3}$ receptor blockade than patients with a high BP_p, particularly regarding positive symptoms; and (2) high striatal dopamine $D_{2/3}$ receptor occupancy is associated with deterioration of a patient's functioning and subjective well-being.

Methods

The study was conducted in accordance with the Declaration of Helsinki II and approved by the Danish National Committee on Biomedical Research Ethics (H-D-2008–088). Written informed consent was obtained from all participants.

Participants

Thirty-two first-episode patients, aged 18–45 years, meeting the International Classification of Diseases, 10th revision (ICD-10) criteria for schizophrenia were recruited from the Capital Region of Denmark as part of a large, multimodal longitudinal study on antipsychotic-naïve first-episode schizophrenia patients (the Pan European Collaboration Antipsychotic-Naive Studies [PECANS]). There is a partial overlap between the participants in the present study and participants in previously published

articles from the PECANS study on different modalities regarding reward processing[48,49] and psychophysiology.[50]

A structured diagnostic interview (Schedule of Clinical Assessment in Neuropsychiatry [SCAN], version 2.1) was performed to verify the diagnosis. None of the patients included in the study had ever been treated with antipsychotic medications or methylphenidate. Patients in antidepressant treatment were either excluded or taken out of their medication 1 month prior to baseline examinations. Other exclusion criteria were serious head traumas, neurological diseases, developmental disorders, pregnancy, and drug dependency (according to ICD-10). Twenty-eight HC matched by gender, age, and parental socioeconomic status were recruited through advertisement. The exclusion criteria were the same as for the patients, and also included former or current psychiatric illnesses, drug abuse or psychiatric diagnosis among first-degree relatives. Urine samples were used for drug screening (Rapid Response, Jepsen HealthCare) for all participants prior to the SPECT scanning.

Four patients and 2 HC were excluded from all analyses. Two patients were excluded due to technical problems with the SPECT image acquisition and one was diagnosed with severe major depressive disorder with psychotic features (DF 32.3) just after baseline examinations. Since conflicting results exist for the association between D$_{2/3}$ receptor availability and cannabis,[51,52] we also excluded one patient due to positive cannabis screenings before the SPECT scans. The excluded HC both received antidepressants at a later 6-month follow-up examination. Four patients discontinued the study and an additional 3 patients were not included at follow-up; see supplementary material. The patients who discontinued the study were not significantly more ill based on the Positive and Negative Syndrome Scale (PANSS). Thus, the complete dataset consisted of 28 patients, 26 HC at baseline and 21 patients at follow-up.

Medication

Treatment with amisulpride was started up in the patients after the baseline examinations. Amisulpride was chosen as the "tool compound" due to its relatively selective D$_{2/3}$ receptor antagonistic effects.[53] The dosage was slowly increased and individually adjusted according to the clinical impression of symptoms and complaints of adverse effects. No medical treatment against adverse effects was allowed. Follow-up examinations were done after 6 weeks of treatment. No adjustment to the dose was allowed in the last week prior to follow-up examinations.

Clinical Measures

In the patient group, psychopathology was assessed with PANSS.[54] Subjective experience of well-being and functioning were assessed with the short form of the SWN (SWNS)[55] and global assessment of functioning (GAF), respectively. We used both the GAF symptom score (GAF-S) and the GAF functioning score (GAF-F). Adverse effects were rated with the Extrapyramidal Symptom Rating Scale[56] (supplementary material).

The change in PANSS scores was calculated as a percentage change between scores at follow-up and baseline. Patients responding to treatment were defined as having an improvement of PANSS positive score of more than 30% similar to a previous study by Meisenzahl et al.[57]

SPECT Acquisition

SPECT data were obtained with a Siemens Symbia T2 series SPECT•CT scanner with low energy high-resolution collimators (full width at half-maximum 7.4 mm) and two-slice CT. The ligand, (S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-iodo-6-methoxybenzamide ([^{123}I]-IBZM) was chosen due to its selectivity for striatal D$_{2/3}$ receptors.[58,59] All participants received 185 mBq [^{123}I]-IBZM per scanning (GE Healthcare). The SPECT scanning was performed using the constant infusion technique.[60,61] A CT scout and 2×30 min tomography were performed. The individually adjusted dose of amisulpride was administered to all patients at same time, 3 h prior to the SPECT scanning at follow-up.

Plasma free fraction of [^{123}I]-IBZM was determined using ultrafiltration (Centrifree, 30 000 MW).[62] The plasma metabolite analysis of [^{123}I]-IBZM was performed using Oasis WCX (Waters) solid phase extraction units and stepwise elution with water, 40% acetonitrile and acidified 95% methanol. The native compound was eluted in the water phase and the metabolites in the subsequent elution.

All participants had a structural MRI scan performed for co-registration. The HC were only scanned at baseline to reduce the radiation dose.

Note that the supplementary material contains the details of the SPECT and MRI acquisitions.

Image Analyses

SPECT images were reconstructed with scatter correction and CT-based attenuation correction using Flash 3D iterative reconstruction (4 subsets, 8 iterations, Gaussian filter 9 mm) on a Siemens syngo workstation (software version VA60B). The 2 [^{123}I]-IBZM tomographies were summed and activity measurements were decay-corrected to the time of the radioligand injection. The CT image from the SPECT scanning and the MRI image were co-registered using the statistical parametric mapping (SPM8) method. The result of the SPM co-registration was then carefully inspected in all 3 planes and, if needed, adjusted manually using a local implementation of an image overlay method.[63] The information from the co-registration between CT and MRI images was used

for co-registration between SPECT and MRI. Inspection and manually adjustments were repeated if needed.

Regions of interest were defined using the high resolution structural MR images and automatically applied to the co-registered SPECT image using a volume-of-interest brain template.[64] We focused on the caudate and chose the cerebellum as the reference region.[65]

Data Analysis and Statistics

BP_p was used as a measure of the regional dopamine $D_{2/3}$ receptor density available for $[^{123}I]$-IBZM binding. BP_p refers to the steady-state ratio of specifically bound radioligand to that of total parent radioligand in plasma.[66] The occupancy was calculated as:

$$Occupancy(\%) = \left(1 - \frac{BP_p(treatment)}{BP_P(baseline)}\right) \times 100\%$$

IBM SPSS version 20 statistics was used for the statistical analyses. For the between group comparison, an independent t-test was used when appropriate, and Mann-Whitney U test when there was evidence of nonnormal distribution. The repeated measures ANOVA analyses were carried out with an approximate normal distribution and with group and gender used as betweensubjects factors when means of the BP_p were compared. Paired t-test was used when baseline measurements were compared with follow-up data. Spearman's correlation coefficient was used in the analyses, though the correlations between BP_p and change in PANSS scores, GAF and SWNS were analysed using general linear modelling techniques.

Results

Demographic and Clinical Data

The patient group did not differ significantly by gender, age, or handedness from the HC group. The 2 groups did, though, differ on smoking habits; table 1.

SPECT Data, Baseline

There were no significant differences in BP_p (total, left or right caudate) between patients and HC at baseline; table 2.

Follow-Up Data

The difference between baseline and follow-up measures of BP_p, GAF, SWNS, and PANSS in patients was all significant. BP_p decreased. PANSS, GAF, and SWNS scores all improved. The PANSS negative score did not change significantly; table 1.

Correlations Between BP_p and Treatment Response

Since clinical follow-up was available for a few patients without follow-up SPECT, 24 patients were included in the analyses.

Significant positive correlations were found between baseline BP_p of the caudate and the change in PANSS score in the total patient group. Patients with a low BP_p had a better treatment response. The correlations were significant for PANSS positive ($P = .048$, $r^2 = .166$); PANSS general ($P = .011$, $r^2 = .257$); and PANSS total ($P = .003$, $r^2 = .342$) but nonsignificant for PANSS negative scores ($P = .328$); figure 1. The 2 patients with a worsening of positive symptoms (filled circles in figure 1) had very low PANSS positive scores at baseline. One was also treated with a low dose of amisulpride (50 mg). Omitting them from the regression strengthened the results ($P = .014$, $r^2 = .268$).

No significant correlations between BP_p at baseline and percentage change in either GAF or SWNS were found.

We also compared patients responding to treatment (defined as an improvement of PANSS positive ≥30%) ($n = 13$, $f = 5$, $m = 8$) to patients not responding ($n = 11$, $f = 7$, $m = 4$). Responders had a significantly lower BP_p (mean BP_p 2.2 vs 3.3 in the caudate, $P = .003$); a lower GAF-F (mean 37 vs 51, $P = .002$); and a lower GAF-S score (mean 37 vs 46, $P = .028$) at baseline. The responders had, per definition, a significantly higher improvement on the PANSS positive, but also on the PANSS general and total score compared to non-responders. Furthermore, responders and nonresponders were found to have similar baseline PANSS scores. The responders improved more on the GAF-S compared to nonresponders; however, they did not improve more on the GAF-F and SWNS. In secondary analyses, we also tested whether the groups or results changed if the rescaled PANSS positive scale ($PANSS_{0-6}$) was used. Responders were then defined as having an improvement on $PANSS_{0-6}$ positive ≥50%.[68,69] One male patient moved to the nonresponder group; the results were otherwise similar.

Correlations at Follow-Up

The mean daily dose of amisulpride was 238 (SD 120) mg and was well correlated with the serum level of amisulpride [(S)-amisulpride] ($P < .001$). We did not find any correlations between caudate BP_p at baseline and the optimal dose needed to obtain clinical effect. The dose of amisulpride and (S)-amisulpride were significantly correlated with the occupancy ($P = .003$ and $P < .001$); supplementary material. There were no significant correlations between the dose [or (S)-amisulpride] and change in PANSS, change in SWNS or change in GAF. Consistent with these findings we did not find any significant correlations between the occupancy and change in PANSS, SWNS, or GAF. The occupancy was significantly negatively correlated with GAF-F, however, at follow-up

Table 1. Demographic Data and Psychopathology

Baseline		N	Mean	SD	Range
Female/male	Schz.p	14/14			
	HC	13/13			
Age (years)	Schz.p	28	23	4.4	18 to 37
	HC	26	23	4.7	18 to 38
Hand-score	Schz.p	28	64	57	−88 to 100
	HC	24	61	62	−100 to 100
DUI (weeks)			69	88	2 to 312
GAF-S			40	9.3	25 to 61
GAF-F			42	11.9	30 to 75
SWNS total		24	67	13.7	41 to 88
PANSS positive			20	3.6	10 to 29
PANSS negative			20	7.7	7 to 38
PANSS general			41	8.4	22 to 56
PANSS total			81	15.3	39 to 102
Follow-up		24			
Female/male		12/12			
GAF-S		23	57[a]	8.6	37 to 80
GAF-F		23	56[a]	12.6	32 to 75
SWNS total			76[a]	12.7	44 to 99
PANSS positive			14[a]	3.5	7 to 20
PANSS negative			20	6.1	9 to 33
PANSS general			31[a]	7.3	18 to 48
PANSS total			65[a]	13.8	40 to 100
Dose (mg)			238	120	50 to 500
(S)-amisulpride (ng/ml)			392	290	15 to 1013
Diagnosis no.		28			
DF.20.0 paranoid		19			
DF.20.1 disorganised		3			
DF.20.3 undifferentiated		3			
DF.20.9 unspecified		3			
SES (A/B/C)	Schz.p	28	4	12	8
	HC	25	5	16	4
Tobacco	Schz.p	28	61% smokers		
	HC	24	25% smokers		

Note: DUI, duration of untreated illness; GAF-F, global assessment of functioning—functioning score; GAF-S: global assessment of functioning—symptom score; HC, healthy controls; PANSS, positive and negative syndrome scale; Sch.p, schizophrenia patients; SD, standard deviation; SES,Parental socioeconomic status (A:high/B:moderate/C:low); SWNS, Subjective Well-Being under Neuroleptics Scale, short version. DUI was calculated from the time a patient experienced a continuous invasive deterioration of functioning due to psychosis-related symptoms.[75]
[a]Significant difference from baseline.

(P = .049; Spearman's rho = −.446). Since we only had a hypothesis regarding GAF and not the specific GAF-F score, this finding is more explorative, but may suggest that the more the dopamine receptors were blocked, the worse the functioning; figure 2.

Supplementary Analyses

There was no significant correlation between BP$_p$ and PANSS, SWNS, GAF scores, and DUI at baseline.

Discussion

As expected, we found a significant negative correlation between the BP$_p$ of the caudate at baseline and clinical improvement of positive symptoms in 24 antipsychotic-naïve first-episode schizophrenia patients after 6 weeks of treatment with the relatively selective D$_{2/3}$ antagonist amisulpride. Additionally, the fact that the patients with a good response had significantly lower baseline D$_{2/3}$ BP$_p$ compared to nonresponders, even though the groups' PANSS baseline scores did not differ, supports baseline D$_{2/3}$ BP$_p$ as a potential marker for treatment outcome. The latter finding mentioned underlines the inability to differentiate good and poor responders based on baseline PANSS scores.

Our findings of a lower baseline BP$_p$, interpreted as higher synaptic dopamine, that correlates with better 6 weeks medication response on positive symptoms are consistent with the previously mentioned study by Abi-Dargham et al,[20] where an association between elevated

Table 2. SPECT Data

Baseline		N	Mean	SD	Range
BP_p total caudate	Schz.p	28	2.9	1.1	1.5–5.6
	HC	26	2.7	0.7	1.6–4.3
BP_p left caudate	Schz.p		2.9	1.1	1.6–5.8
	HC		2.9	0.7	1.6–4.5
BP_p right caudate	Schz.p		2.9	1.2	1.3–5.6
	HC		2.6	0.8	1.5–4.3
Follow-up					
BP_p total caudate		22	1.3[a]	0.7	0.3–2.5
BP_p left caudate			1.3[a]	0.7	0.4–3.0
BP_p right caudate			1.2[a]	0.7	0.3–2.6
Occupancy total caudate (%)			52	19	15–84
Occupancy left caudate (%)			50	20	7–85
Occupancy right caudate (%)			55	21	17–83

Note: BP_p, binding potential; HC, healthy controls; Schz.p, schizophrenia patients; SD, standard deviation.
[a]Significant difference from baseline.
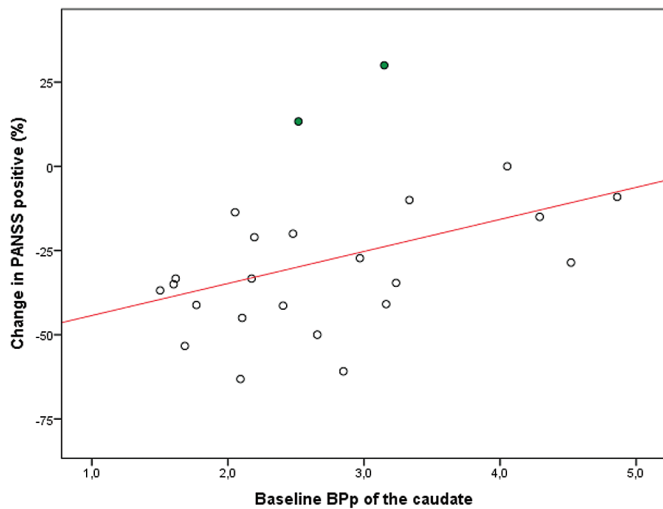
Fig. 1. Relationship between binding potential of the caudate and change in Positive and Negative Syndrome Scale positive score in the patient group. $N = 24$; $R^2 = .166$; $P = .048$.
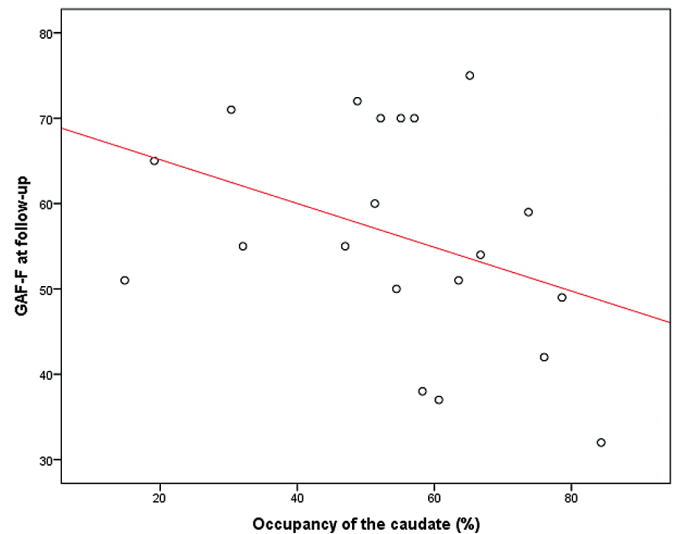

Fig. 2. Correlation between occupancy and functioning by global assessment of functioning—functioning score. A first-order linear approximation is included in the figure solely to illustrate the sign of correlation. $N = 20$; Spearman's rho $= -.0446$; $P = .049$.

synaptic dopamine and greater improvement of positive symptoms was demonstrated in 14 unmedicated patients after treatment with different antipsychotics. The present data are also in line with Demjaha et al's[11] study that shows a higher dopamine synthesis capacity in 12 responders vs 12 nonresponders to antipsychotic treatment. Together these studies indicate a variance in the dopamine disturbances with some patients having a high level of subcortical dopamine.

We chose to define responders based on an improvement on the PANSS positive score of more than 30%. This was in accordance with the study of Meisenzahl et al.[57] However, we obtained a similar division in our patients—and the same results—if we defined the responders with a 50% improvement on the $PANSS_{0-6}$.[67,68] The responders improved significantly more on both the

PANSS positive, total and general scales, although neither responders nor non-responders had any improvement of the negative symptoms. Not surprisingly, the responders also improved significantly more on GAF-S than nonresponders, although no significant differences were found regarding the change in GAF-F and SWNS. These findings suggest that even if patients experience a relief of positive symptoms, their level of functioning and well-being might not improve. A longer follow-up period would of course be necessary to make firm conclusions regarding final remission and recovery, but the present data emphasize the importance of considering improvement of positive symptoms vs adverse effects, particularly secondary negative symptoms from antipsychotic treatment.

Since the patients were all drug naïve a relatively low mean dose of amisulpride (238 mg) was used in the present study. Dose and (S)-amisulpride were, as expected, well correlated with striatal occupancy. We observed a maximum occupancy of 80%. Even if the individually adjusted dose of amisulpride was administered to all patients at same time, we did not find any associations between the striatal occupancy and improvement on the PANSS, SWNS, or GAF. This is consistent with another [123I]-IBZM SPECT study of amisulpride.[57]

Significant correlations between striatal occupancy and outcome have, however, been supported by other PET and SPECT studies[16,17,69–72] correlating striatal occupancy with improvement on the Brief Psychiatric Rating Scale, the PANSS positive and the Clinical Global Impression Scale. Possible explanations for the conflicting results are the different compounds and methodology used in the studies, small sample sizes, inclusion of a mix of schizophrenia patients and patients with schizophreniform disorder, and partly previously medicated patients. Moreover, these studies included patients with motor adverse effects and striatal occupancies above threshold, ie, the studies had a broader range in occupancy. Moreover, in several of the studies occupancy was calculated from baseline BP obtained from different subjects or from a subgroup of the patients. In the present study, BP$_p$ was measured at baseline in the antipsychotic-naïve state and at follow-up, which due to inter-individual differences gives a more precise estimate. Furthermore, our sample size was rather large, homogeneous and included only first-episode schizophrenia patients.

The present data did not replicate the previously mentioned findings of a negative correlation between the striatal occupancy and SWNS at follow-up. We did, however, find a negative correlation between striatal occupancy and functioning on the GAF-F score at follow-up. This could suggest that the more the dopamine receptors are blocked, the worse the functioning, which support the precaution we need to be aware of in treating patients.

Limitations and Strengths of the Data

Given that the antipsychotic-naïve patients had to go through an extensive examination programme we risk ending up with only the mildest cases. Even so, the patients included were moderately to severely ill with a total PANSS score of 81. Patients and controls in our study were not matched for smoking. The relationship between tobacco and enhancement of dopamine transmission has been reported, however changes in human studies are modest (5%–10%) and comparable to test-retest variability.[73] A recent PET study did not find any significant effect of moderate smoking synthesis capacity in the striatum.[74] Moreover, schizophrenia patients have a higher use of tobacco than HC, which is why matching for smoking would have added bias to either the patient or the HC group. Also, our primary outcomes were

analyses within the patient group and these analyses were not affected by the lack of matching for smoking.

A few patients received a small amount of benzodiazepines during hospitalization, but none did so regularly and benzodiazepines were not allowed 12 h prior to any of the examinations. Three patients, though, received benzodiazepine the evening prior to the baseline SPECT scan, and 2 of them had positive urine tests prior to the scan. Another limitation in the study was the spatial resolution of the SPECT images. Choosing an anatomic subdivision of striatum precludes identification of the total associative striatum. We focused on the caudate because PET imaging has identified the head of the caudate as the site of greatest dopamine excess in schizophrenia,[8,9] and we assumed that our spatial resolution was sufficient to distinguish the caudate from the putamen.

The strengths of the study are: inclusion of solely antipsychotic-naïve schizophrenia patients never previously exposed to antipsychotic compounds, the relatively large sample size, the longitudinal study design and the fact that the patients all went through a standardized treatment using antipsychotic monotherapy with a relatively selective D$_{2/3}$ receptor antagonist (amisulpride).

Conlusion

The present data demonstrate a significant correlation between caudate D$_{2/3}$ BP$_p$ and treatment response in a relatively large group of antipsychotic-naïve schizophrenia patients where low BP$_p$ associates with a better treatment response. Psychopathology at baseline did not predict treatment response and no associations between striatal D$_{2/3}$ occupancy and clinical improvement were found. Finding possible prediction markers of treatment response would spare patients ineffective treatment and unnessecary adverse effects. Our findings are in agreement with the hypothesis of an association between treatment response to dopamine blockade and a hyperdopaminergic profile in the patients.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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