

D₂ Receptor Occupancy During High- and Low-Dose Therapy with the Atypical Antipsychotic Amisulpride: A ¹²³I-Iodobenzamide SPECT Study

Christian la Fougère, MD¹; Eva Meisenzahl, MD²; Gisela Schmitt, MD²; Jan Stauss, MD¹; Thomas Frodl, MD²; Klaus Tatsch, MD¹; Klaus Hahn, MD¹; Hans-Jürgen Möller, MD²; and Stefan Dresel, MD¹

¹Department of Nuclear Medicine, University of Munich, Munich, Germany; and ²Department of Psychiatry, University of Munich, Munich, Germany

Amisulpride appears to be an effective agent for treating positive or negative symptoms of schizophrenia, depending on dose. The aim of this study was to assess striatal dopamine D₂ receptor availability by means of ¹²³I-iodobenzamide (IBZM) SPECT in patients treated with high and low doses of this atypical antipsychotic drug. **Methods:** Twenty-nine patients (19 men and 10 women, age range, 19–68 y) with schizophrenia treated with high doses (15 patients; 400–1,200 mg/d; mean dose, 666.7 ± 219.3 mg/d) or low doses (14 patients; 50–300 mg/d; mean dose, 228.6 ± 93.5 mg/d) of amisulpride were examined. For assessment of plasma amisulpride concentration, blood samples were taken. Brain SPECT was performed 2 h after intravenous injection of 185 MBq of ¹²³I-IBZM. For semiquantitative evaluation, transverse slices corrected for attenuation (Chang's first-order method) were used to calculate specific binding in the striatum, with the frontal cortex used as background. **Results:** In all patients treated with amisulpride, specific binding of ¹²³I-IBZM to D₂ receptors was significantly lower ($P < 0.001$) than in healthy controls (0.95). Both groups treated with amisulpride differed significantly in specific binding of ¹²³I-IBZM to dopamine D₂ receptors (0.20 vs. 0.31, $P < 0.05$). D₂ receptor blockade correlated well with the administered dose of amisulpride and with amisulpride plasma concentration. **Conclusion:** Our findings suggest that amisulpride treatment leads to a significant occupancy of postsynaptic dopamine D₂ receptors. The blockade of D₂ receptors tends to be significantly lower in patients receiving low-dose amisulpride therapy than in patients receiving high-dose therapy.

Key Words: ¹²³I-IBZM SPECT; schizophrenia; amisulpride

J Nucl Med 2005; 46:1028–1033

Schizophrenia is a chronic, severe, and disabling brain disorder. With a remarkably constant 1% worldwide lifetime incidence, schizophrenia is one of the most common mental illnesses (1) and results in enormous costs to society.

Received Sep. 17, 2004; revision accepted Feb. 14, 2005.
For correspondence or reprints contact: Stefan Dresel, MD, Department of Nuclear Medicine, Ludwig-Maximilians-University of Munich, Ziemssenstrasse 1, 80336 Munich, Germany.
E-mail: stefan.dresel@med.uni-muenchen.de

Since the advent of conventional antipsychotic medications in the mid-1950s, the outlook has greatly improved for individual patients through reduction of the psychotic symptoms of schizophrenia and amelioration of the prognosis. These drugs, given at usual doses, may exert their therapeutic action on positive symptoms of schizophrenia by decreasing the dopaminergic activity mediated by the affinity for dopamine D₂ receptors (2). Unfortunately, antipsychotic medications such as haloperidol are often associated with a wide range of undesired side effects (3), including parkinsonism, anticholinergic adverse effects, dystonia, and risk of tardive dyskinesia. Since the early 1990s, new neuroleptic medications, such as clozapine, olanzapine, and risperidone, have been introduced. Termed *atypical*, these agents represent a new generation of antipsychotics characterized by a significantly lower incidence of extrapyramidal side effects (EPS) and little or no effect on prolactin levels. The exact mechanisms that make these drugs atypical are not well understood (4). One important aspect of the pharmacologic profile of atypical neuroleptics, compared with conventional neuroleptics, is a higher affinity for 5-hydroxytryptamine type 2 (5-HT₂) than for D₂ receptors (5). Because of their superior therapeutic efficacy, tolerability, and safety profiles, compared with those of classic neuroleptics, atypical antipsychotic agents are considered to be the treatment of choice in first-episode patients (6).

Amisulpride is a substituted benzamide derivative highly predictive of potent antipsychotic activity with a low potential to cause EPS (7). It is considered to bind selectively and distinctly to the D₂ and D₃ dopaminergic receptors (8). Animal studies and clinical evidence suggest that the efficacy of amisulpride for treating negative or positive symptoms of schizophrenia may be dose dependent (2,9). At high doses (400–1,200 mg/d), amisulpride is used to treat acute symptomatology and positive symptoms in patients with schizophrenia. Furthermore, beneficial effects on negative symptoms in schizophrenic patients with a predominantly deficient syndrome have been demonstrated with lower doses of up to 300 mg/d (8).

As previously reported, dopamine D₂ receptors can be adequately studied *in vivo* using SPECT, applying the benzamide derivative ¹²³I-iodobenzamide (IBZM). This radiopharmaceutical crosses the blood–brain barrier and selectively binds to the postsynaptic dopamine D₂ and D₃ receptors (10). The aim of this study was to evaluate the degree of D₂ receptor occupancy in schizophrenic patients treated with high and low antipsychotic dosages.

MATERIALS AND METHODS

Twenty-nine patients aged 19–68 y (mean age ± SD, 32 ± 12 y) with schizophrenia or schizoaffective disorder (DSM-IV) being treated with the atypical antipsychotic amisulpride were investigated. Fifteen patients (9 men and 6 women) received high doses of amisulpride (400–1,200 mg/d; mean dose, 666.7 ± 219.3 mg/d), and 14 other patients (10 men and 4 women) were treated with low, steady doses (50–300 mg/d; mean dose, 228.6 ± 93.5 mg/d) of amisulpride during 13.4 ± 2.4 d. On the day of the SPECT investigation, no amisulpride medication was given. The last dose of medication was administered in the hospital ward on the evening before the day of scintigraphy. Concomitant medication was restricted to biperiden and zopiclone. The literature shows no evidence that these concomitantly administered drugs affect the binding of IBZM to the dopamine D₂ receptor (11). For patients pretreated with classic neuroleptics, 3 d were allowed for washout of prior neuroleptic treatment before monotherapy with amisulpride began. In 28 of 29 patients, plasma levels of amisulpride were assessed just before the SPECT investigation. Each subject received 185 MBq of ¹²³I-IBZM intravenously 12–14 h after taking the last dose of amisulpride. Two hours after radiotracer administration, SPECT images were acquired during a period of 50 min. SPECT images were acquired using a Prism 3000 XP triple-head γ-camera (Picker) equipped with high-resolution fanbeam collimators. The acquisition parameters included a 20% energy window centered on 159 keV, a rotational radius of 13 cm or less, 120 projection angles over 360°, and a 128 × 128 matrix with a pixel width of 2.11 mm in the projection domain. The projection images were reconstructed by filtered backprojection and filtered by a low-pass filter. For uniform attenuation correction, Chang's first-order method was used. Images were uniformly resliced using a line drawn to connect the most anterior aspect of the frontal pole to the most posterior aspect of the occipital pole, which approximates the line connecting the anterior and posterior commissures. The control group was 10 healthy age- and sex-matched subjects (6 men and 4 women; mean age, 32 y; range, 22–58 y).

To assess specific tracer uptake in the striatum, we used the region-of-interest technique. In each patient, data were evaluated for the 2 consecutive transverse slices showing the highest tracer accumulation in the basal ganglia; afterward, the arithmetic mean of these 2 slices was calculated. Mean specific binding in the basal ganglia regions was calculated by subtracting the mean counts per pixel in the frontal cortex as background (BKG) from the basal ganglia region (STR) and dividing the results by the mean counts per pixel in the background ($(STR - BKG)/BKG$). Templates were used for defining the striatal regions of interest. The size and shape of the templates were established and optimized using the data of the control group. The nonspecific background activity was estimated by drawing a region of interest around the frontal cortex. Mean specific binding (SB) values of a healthy control group were used to calculate the percentage occupancy of striatal dopamine D₂

receptor ($(SB_{control} - SB_{patient})/SB_{control}$). For statistical analyses, ANOVA, regression analyses (least-squares method), and the Student *t* test were used. All values were normally distributed. Data were compared with those of the control group. Differences were considered to be statistically significant when *P* was <0.05 and highly significant when *P* was <0.001.

RESULTS

The high-dose amisulpride group was significantly different from the low-dose group in administered dosage (8.8 ± 3.6 mg/kg of body weight vs. 3.2 ± 1.3 mg/kg of body weight, *P* < 0.001; total dose, 666.7 ± 219.3 mg/d vs. 228.6 ± 93.5 mg/d, *P* < 0.001). The measured amisulpride plasma concentrations were 257.7 ± 217.3 μg/L in the high-dose group and 134.2 ± 101.3 μg/L in the low-dose group. Specific binding of ¹²³I-IBZM to the striatal dopamine D₂ receptor was significantly lower (*P* < 0.001) in all patients undergoing low-dose therapy (0.31 ± 0.11) or high-dose therapy (0.20 ± 0.12) with amisulpride than in untreated healthy controls (0.95 ± 0.10). The estimation of dopamine D₂ receptor occupancy by amisulpride indicated a mean of 73.3% ± 13.7% and a range of 41.9%–100% (*P* < 0.001). A significant difference was found between the high-dose group (mean D₂ occupancy, 79.1% ± 12.9%; range, 51.3%–100%) and the low-dose group (mean D₂ occupancy, 67.1% ± 12.1%; range, 41.9%–100%, *P* < 0.05). Individual indices for dopamine D₂ receptor occupancy are presented in Table 1. Figure 1 shows the specific binding of ¹²³I-IBZM to the dopamine D₂ receptors in untreated healthy controls and treated schizophrenic patients. A good dose–response relationship between dopamine D₂ receptor occupancy and daily dose of amisulpride (*r* = 0.72; *P* < 0.001) was observed, as shown in Figure 2. A similar correlation between amisulpride plasma concentration and binding of ¹²³I-IBZM to striatal dopamine D₂ receptors was observed (*r* = 0.65; *P* < 0.001), as shown in Figure 3. Figure 4 shows typical images of patients treated with different doses of amisulpride.

DISCUSSION

The objective of the present study was to assess striatal dopamine D₂ receptor occupancy in 29 patients with schizophrenia and schizoaffective disorder under high- or low-dose treatment with the atypical antipsychotic amisulpride, as measured by ¹²³I-IBZM SPECT. The clinical utility of this method to measure brain dopamine receptor occupancy in healthy volunteers, in patients with diverse neuropsychiatric disorders, and in schizophrenic patients receiving different types of antipsychotic medication has previously been reported by several investigators (12–20), despite the fact that SPECT studies cannot quantify results as well as can PET studies.

It is thought that dopamine D₂ receptor blockade mediates the antipsychotic action of typical neuroleptics such as haloperidol. This hypothesis has been confirmed in various

TABLE 1
Mean Dosages of Amisulpride and Background-Corrected D₂ Receptor Binding

Patient no.	Dosage of amisulpride (mg/d)	Dosage of amisulpride (mg/kg of body weight/d)	Plasma concentration of amisulpride (μg/L)	D ₂ receptor occupancy*
1	50	0.81	77	41.9
2	100	1.55	27	50.1
3	100	1.74	128	60.3
4	150	1.70	120	58.3
5	200	2.67	108	75.9
6	200	2.95	104	65.5
7	300	3.28	—	67.6
8	300	3.79	84	66.5
9	300	3.80	145	78.9
10	300	4.06	118	71.9
11	300	4.14	55	68.6
12	300	4.17	312	82.9
13	300	4.25	82	65.0
14	300	5.17	385	85.9
15	400	4.65	88	51.3
16	400	5.01	179	81.7
17	400	5.70	184	77.0
18	500	6.75	421	81.7
19	500	8.65	114	79.5
20	600	6.32	177	92.1
21	600	8.05	121	66.1
22	600	9.69	219	79.4
23	800	6.58	169	77.8
24	800	8.51	64	87.8
25	800	10.13	223	60.6
26	800	10.61	263	87.4
27	800	10.81	518	100.0
28	800	11.51	261	70.5
29	1,200	19.20	910	93.4

* $(SB_{\text{control}} - SB_{\text{patient}})/SB_{\text{control}}$.

studies with PET and SPECT (19,21). In defining the atypicality of antipsychotics, however, some experts include not only the criterion of no or lower risk of inducing EPS coupled with enhanced improvement in negative symptoms but also efficacy in schizophrenic patients refractory to treatment with classic neuroleptics, or lack of drug-induced hyperprolactinemia (22). Evidence presently suggests that atypical drugs differ from the typical in their mechanism of action but that not all share the same mechanism (23).

In contrast to other atypical antipsychotics, the substituted benzamide derivative amisulpride binds selectively and distinctly to the dopaminergic D₂ and D₃ receptors without substantial affinity to D₁ or serotonergic 5-HT₂ receptors (8). Several studies have demonstrated a biphasic effect of amisulpride on positive and negative symptoms, depending on the administered dose range (24–26), accompanied by a low incidence of EPS (9). The physiologic mechanism of amisulpride and its dose–response relationship has not, to date, been definitely explained. One hypoth-

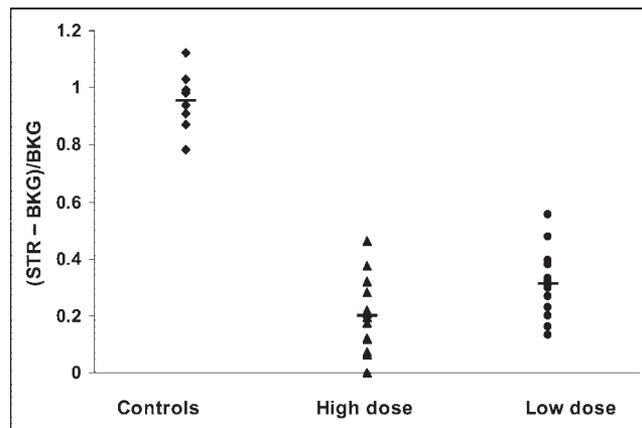


FIGURE 1. Specific binding ($[STR - BKG]/BKG$) of ^{123}I -IBZM in healthy controls and in schizophrenic patients treated with high or low doses of amisulpride.

esis is that its clinical efficacy against negative symptoms may be explained by blockade of presynaptic dopaminergic D₂ and D₃ autoreceptors that control dopamine release at low doses, whereas at higher doses, amisulpride occupies postsynaptic dopamine D₂ receptors (27,28). To date, 2 PET studies (2,29) have reported striatal binding indices in patients treated with amisulpride. Martinot et al. reported a low postsynaptic D₂ occupancy in the striatum at low doses of amisulpride (50–100 mg/d). The authors also suggested that extrastriatal binding could mediate the effect on negative symptoms (2). At amisulpride doses resulting in low plasma levels, no apparent interaction of amisulpride with the striatum was detectable by Xiberas et al. (29). The authors hypothesized that low plasma concentrations are associated with low striatal binding and marked extrastriatal binding, in contrast to marked binding in both striatal and extrastriatal regions for higher plasma concentrations (29).

Our study found a clear correlation between the degree of striatal dopamine D₂ receptor occupancy and the amisulpride plasma concentration and a quite similar correlation between the degree of striatal dopamine D₂ receptor occu-

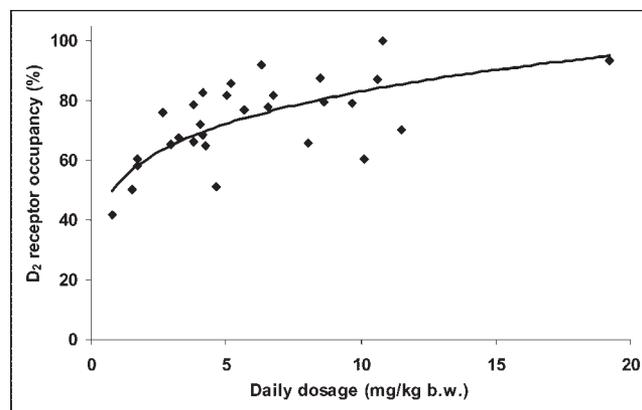


FIGURE 2. Dose–response relationship between striatal dopamine D₂ receptor occupancy ($(SB_{\text{control}} - SB_{\text{patient}})/SB_{\text{control}}$) and daily dose of amisulpride (mg/kg of body weight [b.w.]).

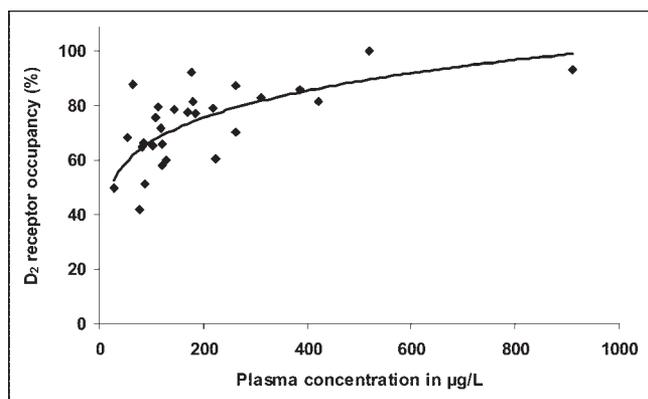


FIGURE 3. Dose–response relationship between striatal dopamine D₂ occupancy ($(SB_{\text{control}} - SB_{\text{patient}})/SB_{\text{control}}$) and amisulpride plasma concentration ($\mu\text{g/L}$).

pancy and the administered dose of amisulpride. Thus, our results are concordant with the findings of other studies that demonstrated positive correlations between the plasma rates of amisulpride and the binding indices in striatal regions (29,30).

At therapeutic doses, the dopamine D₂ receptor occupancy of amisulpride was closer to that of atypical neuroleptics such as olanzapine and risperidone than to that of clozapine, the archetype of atypical neuroleptics, which presented by far the lowest occupancy seen in our studies. The high- and low-dose treatment groups differed significantly in dopamine D₂ receptor occupancy, and binding of ¹²³I-IBZM was significantly lower in both groups than in untreated healthy controls. With regard to differences from the findings of Xiberas et al. (29), their mean administered dosage in the low dose range was explicitly lower (105.6 mg/d) than our average administered low dose (228.6 mg/d). Consequently, we assume that, in our low-dose group, the administered mean daily dose of amisulpride was above the threshold described by Xiberas et al. under which no or only little striatal interaction appeared. Overall dopamine D₂ receptor occupancy in the high-dose group was higher in our study than in other studies (2,20,29), as again may partly be explained by the higher average dose administered to our patients. However, we believe that in view of the described differences in estimation of D₂ receptor occupancy, the use of different methods such as SPECT and PET, and the

consequent use of different radioligands, the accuracy of predicting D₂ occupancy from plasma levels is not assured.

Overall, our findings revealed that at doses considered to be low in our institution, amisulpride had already blocked postsynaptic striatal dopamine D₂ receptors and successfully treated negative symptoms. The different actions of amisulpride dosage on positive and negative symptoms may be due to interactions with other areas of the dopaminergic neurotransmitter systems. A limitation of this study is that the radiopharmaceutical ¹²³I-IBZM provides reliable information about dopaminergic D₂ receptor status in only the striatum and does not allow adequate visualization of extrastriatal D₂ receptors. However, it has been postulated that amisulpride also binds to dopamine receptors in limbic and hippocampal structures. This effect suggests that, compared with typical neuroleptics, ¹²³I-IBZM has a low propensity to induce EPS (30).

Reports in the literature indicate an apparent relationship between the degree of striatal D₂ receptor occupancy, the onset of EPS, and treatment with neuroleptics (19,21,31,32). Atypical neuroleptics such as clozapine are considered to cause fewer EPS than do typical neuroleptics (33), potentially related to their lower striatal dopamine D₂ blockade in vivo (34) and, in part, to their affinity to 5-HT₂ receptors (5). However, also under discussion is that a preferential action on serotonin 5-HT₂ or D₄ receptors or a more rapid dissociation from the dopamine D₂ receptor may explain the atypicality (4,22).

When compared with the findings for olanzapine, clozapine, and risperidone in our previous studies, the findings for amisulpride in the present study revealed a higher dose–response relationship for the former neuroleptics. The low propensity for inducing EPS in patients treated with olanzapine, found in our previous study, (35) can be explained not only by relatively low striatal D₂ receptor blocking but also by other receptor-binding profiles such as affinity to muscarinic receptors or particularly to the 5-HT₂ system (36). However, amisulpride does not have any significant affinity to the 5-HT₂ system or to other nondopaminergic transmitter systems. Therefore, the D₂/5-HT₂ receptor hypothesis cannot explain the atypicality of antipsychotics. Nevertheless, amisulpride clearly has the clinical profile of an atypical antipsychotic, characterized in particular by its lower propensity to induce EPS and its greater efficacy in

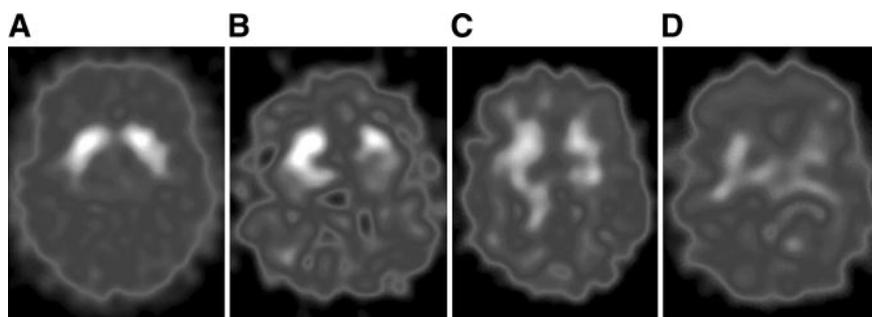


FIGURE 4. ¹²³I-IBZM SPECT images of dopamine D₂ receptor binding at equilibrium: drug-naïve schizophrenic patient (A) and schizophrenic patients being treated with 50 mg (B), 300 mg (C), or 800 mg (D) of amisulpride per day.

treating negative symptoms (22). Thus, the decreased tendency of atypical neuroleptics to induce EPS at therapeutic doses can be considered to be due not only to limited occupancy of striatal dopamine D₂ receptors or to affinity to the 5-HT₂ system in vivo but also, at least partly, to other mechanisms.

Two possible mechanisms that could explain the atypicality of amisulpride in light of these findings were suggested by Schoemaker et al. and include action on limbic D₂/D₃ receptors and preferential blockade of presynaptic D₂/D₃ receptors (22,28). The hypothesis of limbic-selective occupancy of D₂ receptors by amisulpride could be confirmed by the findings of Bressan et al. for ¹²³I-epidepride (30). Otherwise, the “fast-off” theory of antipsychotic action, which postulates a rapid dissociation of atypical antipsychotics from the dopamine D₂ receptors, is discussed in the literature (37). A limitation of this study is that, for ethical reasons, repeated SPECT investigations of schizophrenic patients in drug-naïve periods or while receiving amisulpride medication could not be performed. Dopamine D₂ receptor binding has been assessed by PET and SPECT in untreated schizophrenic patients in several studies, with inconsistent results (38–41). In view of the results of 2 published ¹²³I-IBZM studies that found no significant differences in D₂ receptor availability between patients with schizophrenia and a comparison group (38,42), and for better comparison with previously published studies, we expressed D₂ receptor occupancy in relation to our standardized control population.

CONCLUSION

The findings of the present study indicated that low-dose therapy with the atypical antipsychotic agent amisulpride is associated with a significantly lower blockade of striatal dopamine D₂ receptors than is seen during high-dose treatment. However, a significant striatal D₂ blockade was demonstrated at therapeutically effective dose ranges. Furthermore, this study showed a good relationship between the degree of striatal dopamine D₂ receptor occupancy and the amisulpride plasma concentration or the administered dose. The measured striatal D₂ receptor occupancy was as high as that observed in our previous olanzapine and risperidone studies and even explicitly higher than the receptor occupancy observed with clozapine. Further studies with radiotracers of higher affinity than ¹²³I-IBZM, such as ¹²³I-epidepride and ¹⁸F-fallypride, are warranted to assess the role of D₂ occupancy of amisulpride and other atypical antipsychotics in the limbic cortex.

ACKNOWLEDGMENT

We are grateful for the support and superb technical assistance of the technicians in the Department of Nuclear Medicine at the University of Munich.

REFERENCES

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed. Washington, DC: American Psychiatric Association; 1994:273–315.
- Martinot JL, Paillere-Martinot ML, Poirier MF, Dao-Castellana MH, Loc'h C, Maziere B. In vivo characteristics of dopamine D₂ receptor occupancy by amisulpride in schizophrenia. *Psychopharmacology (Berl)*. 1996;124:154–158.
- Kane JM. Schizophrenia. *N Engl J Med*. 1996;334:34–41.
- Kapur S, Remington G. Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. *Annu Rev Med*. 2001;52:503–517.
- Meltzer HY. The concept of atypical antipsychotics. In: Boer J, Westenberg H, van Praag H, eds. *Advances in the Neurobiology of Schizophrenia*. Chichester, West Sussex, England: Wiley and Sons; 1995:265–273.
- Peuskens J. Switching to amisulpride. *Curr Med Res Opin*. 2002;18:s23–s28.
- Lecrubier Y. Is amisulpride an “atypical” atypical antipsychotic agent? *Int Clin Psychopharmacology*. 2000;15:21–26.
- Blin O. Which role for amisulpride in rehabilitation of schizophrenic patients with acute exacerbation? *Encephale*. 2000;26:7–11.
- Sechter D, Peuskens J, Fleurot O, Rein W, Lecrubier Y. Amisulpride vs. risperidone in chronic schizophrenia: results of a 6-month double-blind study. *Neuropsychopharmacology*. 2002;27:1071–1081.
- Kung HF, Pan SG, Kung MP, et al. In vitro and in vivo evaluation of [¹²³I-123]IBZM: a potential CNS D₂ dopamine receptor imaging agent. *J Nucl Med*. 1989;30:88–92.
- Ebert D, Feistel H, Loew T, Pirner A. Dopamine and depression: striatal dopamine D₂ receptor SPECT before and after antidepressant therapy. *Psychopharmacology (Berl)*. 1996;126:91–94.
- Dresel S, Mager T, Rossmüller B, et al. In vivo effects of olanzapine on striatal dopamine D(2)/D(3) receptor binding in schizophrenic patients: an iodine-123 iodobenzamide single-photon emission tomography study. *Eur J Nucl Med*. 1999;26:862–868.
- Dresel S, Tatsch K, Dahne I, Mager T, Scherer J, Hahn K. Iodine-123-iodobenzamide SPECT assessment of dopamine D₂ receptor occupancy in risperidone-treated schizophrenic patients. *J Nucl Med*. 1998;39:1138–1142.
- Pilowsky LS, Busatto GF, Taylor M, et al. Dopamine D₂ receptor occupancy in vivo by the novel atypical antipsychotic olanzapine: a ¹²³I-IBZM single photon emission tomography (SPET) study. *Psychopharmacology (Berl)*. 1996;124:148–153.
- Pilowsky LS, Costa DC, Eil PJ, Verhoeff NP, Murray RM, Kerwin RW. D₂ dopamine receptor binding in the basal ganglia of antipsychotic-free schizophrenic patients: an ¹²³I-IBZM single photon emission computerized tomography study. *Br J Psychiatry*. 1994;164:16–26.
- Pilowsky LS, O’Connell P, Davies N, et al. In vivo effects on striatal dopamine D₂ receptor binding by the novel atypical antipsychotic drug sertindole: a ¹²³I-IBZM single photon emission tomography (SPET) study. *Psychopharmacology (Berl)*. 1997;130:152–158.
- Scherer J, Tatsch K, Albus M, Schwarz J, Mager T, Oertel WH. D₂-dopamine-receptor occupancy during treatment with haloperidol decanoate. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:104–106.
- Scherer J, Tatsch K, Schwarz J, Oertel W, Kirsch MC, Albus M. Striatal D₂-dopamine receptor occupancy during treatment with typical and atypical neuroleptics. *Biol Psychiatry*. 1994;36:627–629.
- Scherer J, Tatsch K, Schwarz J, Oertel WH, Konjarczyk M, Albus M. D₂-dopamine receptor occupancy differs between patients with and without extrapyramidal side effects. *Acta Psychiatr Scand*. 1994;90:266–268.
- Tauscher J, Kufferle B, Asenbaum S, Tauscher-Wisniewski S, Kasper S. Striatal dopamine-2 receptor occupancy as measured with [¹²³I]iodobenzamide and SPECT predicted the occurrence of EPS in patients treated with atypical antipsychotics and haloperidol. *Psychopharmacology (Berl)*. 2002;162:42–49.
- Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D₁ and D₂ dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. *Arch Gen Psychiatry*. 1992;49:538–544.
- Moller HJ. Amisulpride: limbic specificity and the mechanism of antipsychotic atypicality. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:1101–1111.
- Meltzer HY. What’s atypical about atypical antipsychotic drugs? *Curr Opin Pharmacol*. 2004;4:53–57.
- Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F. Treatment of negative symptoms in schizophrenia with amisulpride. *Br J Psychiatry*. 1995;166:68–72.
- Lecrubier Y. Amisulpride: progress and outcomes. *Curr Med Res Opin*. 2002;18:s18–s22.
- Paillere-Martinot ML, Lecrubier Y, Martinot JL, Aubin F. Improvement of some

- schizophrenic deficit symptoms with low doses of amisulpride. *Am J Psychiatry*. 1995;152:130–134.
27. Perrault G, Depoortere R, Morel E, Sanger DJ, Scatton B. Psychopharmacological profile of amisulpride: an antipsychotic drug with presynaptic D₂/D₃ dopamine receptor antagonist activity and limbic selectivity. *J Pharmacol Exp Ther*. 1997;280:73–82.
 28. Schoemaker H, Claustre Y, Fage D, et al. Neurochemical characteristics of amisulpride, an atypical dopamine D₂/D₃ receptor antagonist with both presynaptic and limbic selectivity. *J Pharmacol Exp Ther*. 1997;280:83–97.
 29. Xiberas X, Martinot JL, Mallet L, et al. In vivo extrastriatal and striatal D₂ dopamine receptor blockade by amisulpride in schizophrenia. *J Clin Psychopharmacology*. 2001;21:207–214.
 30. Bressan RA, Erlandsson K, Jones HM, et al. Is regionally selective D₂/D₃ dopamine occupancy sufficient for atypical antipsychotic effect? An in vivo quantitative [¹²³I]epidepride SPET study of amisulpride-treated patients. *Am J Psychiatry*. 2003;160:1413–1420.
 31. Farde L. Selective D₁- and D₂-dopamine receptor blockade both induces akathisia in humans: a PET study with [¹¹C]SCH 23390 and [¹¹C]raclopride. *Psychopharmacology (Berl)*. 1992;107:23–29.
 32. Farde L, Hall H. Positron emission tomography: examination of chemical transmission in the living human brain—development of radioligands. *Arzneimittelforschung*. 1992;42:260–264.
 33. Moller HJ. State of the art of drug treatment of schizophrenia and the future position of the novel/atypical antipsychotics. *World J Biol Psychiatry*. 2000;1:204–214.
 34. Farde L, Nordstrom AL. PET analysis indicates atypical central dopamine receptor occupancy in clozapine-treated patients. *Br J Psychiatry Suppl*. 1992;17:30–33.
 35. Meisenzahl EM, Dresel S, Frodl T, et al. D₂ receptor occupancy under recommended and high doses of olanzapine: an iodine-123-iodobenzamide SPECT study. *J Psychopharmacol*. 2000;14:364–370.
 36. Schmitt GJ, Meisenzahl EM, Dresel S, et al. Striatal dopamine D₂ receptor binding of risperidone in schizophrenic patients as assessed by ¹²³I-iodobenzamide SPECT: a comparative study with olanzapine. *J Psychopharmacol*. 2002;16:200–206.
 37. Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry*. 2002;47:27–38.
 38. Abi-Dargham A, Gil R, Krystal J, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry*. 1998;155:761–767.
 39. Wong DF, Wagner HN Jr, Tune LE, et al. Positron emission tomography reveals elevated D₂ dopamine receptors in drug-naive schizophrenics. *Science*. 1986;234:1558–1563.
 40. Crawley JC, Crow TJ, Johnstone EC, et al. Uptake of ⁷⁷Br-spiperone in the striata of schizophrenic patients and controls. *Nucl Med Commun*. 1986;7:599–607.
 41. Farde L, Wiesel FA, Stone-Elander S, et al. D₂ dopamine receptors in neuroleptic-naive schizophrenic patients: a positron emission tomography study with [¹¹C]raclopride. *Arch Gen Psychiatry*. 1990;47:213–219.
 42. Laruelle M, Abi-Dargham A, van Dyck CH, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci USA*. 1996;93:9235–9240.





The Journal of
NUCLEAR MEDICINE

D₂ Receptor Occupancy During High- and Low-Dose Therapy with the Atypical Antipsychotic Amisulpride: A ¹²³I-iodobenzamide SPECT Study

Christian la Fougère, Eva Meisenzahl, Gisela Schmitt, Jan Stauss, Thomas Frodl, Klaus Tatsch, Klaus Hahn, Hans-Jürgen Möller and Stefan Dresel

J Nucl Med. 2005;46:1028-1033.

This article and updated information are available at:
<http://jnm.snmjournals.org/content/46/6/1028>

Information about reproducing figures, tables, or other portions of this article can be found online at:
<http://jnm.snmjournals.org/site/misc/permission.xhtml>

Information about subscriptions to JNM can be found at:
<http://jnm.snmjournals.org/site/subscriptions/online.xhtml>

The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

© Copyright 2005 SNMMI; all rights reserved.