

Subjective Experience and D₂ Receptor Occupancy in Patients With Recent-Onset Schizophrenia Treated With Low-Dose Olanzapine or Haloperidol: A Randomized, Double-Blind Study

Lieuwe de Haan, M.D., Ph.D.

Marion van Bruggen, M.D.

Jules Lavalaye, M.D., Ph.D.

Jan Booij, M.D., Ph.D.

Peter M.A.J. Dingemans, Ph.D.

Don Linszen, M.D., Ph.D.

Objective: The authors tested the hypothesis that a dopamine D₂ receptor occupancy level between 60% and 70% in patients with recent-onset schizophrenia would result in optimal subjective experience. In addition, they sought preliminary evidence on whether subjective experience is better with low-dose olanzapine than with low-dose haloperidol.

Method: Subjects (N=24) who met DSM-IV criteria for schizophrenia were randomly assigned to 6 weeks of double-blind treatment with either olanzapine, 7.5 mg/day, or haloperidol, 2.5 mg/day. Subjective experience, psychopathology, and extrapyramidal symptoms were assessed at baseline and at endpoint. After 6 weeks, D₂ receptor occupancy was assessed with [¹²³I]iodobenzamide single photon emission computed tomography.

Results: The two study groups were similar at baseline. After 6 weeks, patients receiving olanzapine had a significantly

lower mean dopamine D₂ receptor occupancy (51.0%, range=36%–67%) than those given haloperidol (65.5%, range=45%–75%). Receptor occupancy between 60% and 70% was associated with optimal subjective experience, and subjective experience improved significantly in the haloperidol group.

Conclusions: A level of D₂ receptor occupancy between 60% and 70% is optimal for subjective experience of patients with recent-onset schizophrenia. Substantial interindividual variation in D₂ receptor occupancy was seen at fixed low-dose levels of olanzapine and haloperidol. Olanzapine, 7.5 mg/day, showed no superior subjective response over haloperidol, 2.5 mg/day. Olanzapine may need to be dosed higher than 7.5 mg/day for most patients with recent-onset schizophrenia, and haloperidol needs to be individually titrated in the very low dose range to reach optimal occupancy.

(*Am J Psychiatry* 2003; 160:303–309)

The debate about optimal dosing of antipsychotic medication is still a lively one. Haase (1) introduced the concept “neuroleptic threshold dose”: a dose at which patients develop minimal extrapyramidal side effects. Exceeding this dose resulted in more extrapyramidal side effects but not in a better response (2). The concept of a “therapeutic window” emerged (3). Since the 1980s, the occupancy of striatal dopamine D₂ receptors and, consequently, the “neuroleptic threshold dose” or “therapeutic window” has been assessed in vivo with scintigraphic techniques (4–6). It has been suggested that a D₂ receptor occupancy threshold in the range of 60%–70% is needed to obtain satisfactory antipsychotic response (7–9). A stepped increase in response was found beyond 65% D₂ receptor occupancy; prolactin elevation became prominent beyond 72%, while extrapyramidal side effects were evident beyond 78% (10).

Dopaminergic neurotransmission also plays an important role in the reward system, and inhibition of this system can be accompanied by reduced motivation, drive,

and spontaneity (11). Occupancy of dopamine receptors by antipsychotic medication is thought to influence a patient's subjective experience (12–15).

We hypothesized that there would also be a “window” for the influence of antipsychotic medication on the subjective experience of patients. In an earlier study, we found that levels of D₂ occupancy lower than those that cause extrapyramidal side effects may be related to negative subjective experience (12). The “subjective side effect window” in dosing antipsychotic drugs may be small. We hypothesized that “optimal occupancy of D₂ receptors” would lie between 60% and 70%. We proposed that D₂ binding should not exceed 70% to avoid excessive inhibition of dopamine neurotransmission, resulting in a negative impact on subjective experience. On the other hand, D₂ occupancy below 60% leaves a patient in a psychotic state (too high a functional level of the dopamine system) accompanied by negative subjective well-being. This line of thought can be compared to the hypothesis about an optimal range in which D₂ receptor stimulation by drugs of abuse can be

perceived as reinforcing: too little may not be sufficient, but too much may have an aversive effect (16).

The subjective experience of patients treated with antipsychotic medication is related to medication compliance (17–19). Moreover, subjectively experienced side effects are more distressing than other side effects (20). Strategies to improve the subjective experience of patients receiving antipsychotic medication are needed to improve compliance and thereby ameliorate the course of schizophrenia.

The development of a new generation of antipsychotic medications could be important in this respect. Olanzapine has been found to be associated with a better subjective experience than typical antipsychotic drugs (21, 22). However, different levels of D₂ occupancy have confounded previous comparisons of antipsychotic drugs (23). If the severity of negative subjective experience is related to D₂ receptor occupancy, then the new antipsychotic medications might not be more beneficial for subjective experience than typical antipsychotic drugs in doses with comparable D₂ receptor occupancy. Therefore, another strategy to improve the subjective experience might be treatment with low-dose typical antipsychotic drugs.

Limitations of earlier studies on subjective experience with typical and atypical antipsychotic medications were the noncomparative dosing and the lack of a randomized double-blind design. We therefore conducted a 6-week, randomized, double-blind study of fixed low-dose olanzapine or haloperidol in young patients with recent-onset schizophrenia. To study the relation between subjective experience and D₂ receptor occupancy by these drugs, we assessed in vivo striatal dopamine D₂ receptor occupancy with [¹²³I]iodobenzamide ([¹²³I]IBZM) single photon emission computed tomography (SPECT).

Method

This prospective, randomized, double-blind study was conducted at the Adolescent Clinic of the Academic Medical Center in Amsterdam, a specialized unit for in- and outpatient treatment of young persons with recent-onset schizophrenia. Local ethics committee approvals were obtained, and subjects gave their written informed consent after a complete description of the study.

Subjects

Male and female patients aged 17–28 years who met DSM-IV criteria for schizophrenia and who had been admitted to the Adolescent Clinic were eligible for recruitment. Discharge diagnoses according to DSM-IV criteria were based on longitudinal clinical assessment. Sources of information were patients, parents, and other significant others (Longitudinal Expert Assessment of Diagnosis procedure) (24). Exclusion criteria were neurological or endocrine disease, mental retardation, the use of adjunctive medications such as mood stabilizers or antidepressants, a history of treatment with clozapine, a history of unresponsiveness to haloperidol or olanzapine, and intramuscular antipsychotic treatment within the last year.

Procedure

Previous medication was diminished during 1 week and then stopped. Olanzapine, 7.5 mg once daily, or haloperidol, 2.5 mg

once daily, was assigned according to a randomized block design. These doses were chosen for their expected D₂ receptor occupancy of 65% (23, 25–27) in patients with previous exposure to antipsychotic medication. This rate of D₂ receptor occupancy is thought to be a threshold above which a satisfactory antipsychotic response can be expected (7–9).

Duration of the double-blind phase was 6 weeks. Only the benzodiazepine oxazepam was allowed as adjunctive medication. Treating physicians made the decision regarding the use of oxazepam on the basis of clinical considerations. The use of oxazepam was indicated for anxiety, agitation, and insomnia.

Assessments

Subjective experience, extrapyramidal side effects, and psychopathology were assessed at baseline and after 6 weeks. The subjective experience of the patients was measured with the Subjective Well-Being Under Neuroleptics Scale (17, 28). This 38-item, self-rating scale assesses through 6-point Likert-type responses the subjective experience over the preceding 7 days. Naber (17) found a five-factor solution of the scale: emotional regulation, self-control, mental functioning, social integration, and physical functioning. (Sample questions: “I am full of energy and life.” “I feel very comfortable in my body.”) In a study of patients with schizophrenia (N=216), the Subjective Well-Being Under Neuroleptics Scale showed good practicability, reliability, and sensitivity (17). We recently replicated these results: 97% of patients with recent-onset schizophrenia (N=105) were capable of reproducing their subjective experience in a consistent way before as well as after medication stabilization. The internal consistency was high (Cronbach's alpha=0.95). The test-retest reliability appeared to be high if medication was not changed, and the Subjective Well-Being Under Neuroleptics Scale appeared to be sensitive for changes in medication or dose (28). Severity of patients' psychopathology was assessed with the Positive and Negative Syndrome Scale, the Montgomery-Åsberg Depression Rating Scale, and the Clinical Global Impression (CGI) scale. Extrapyramidal symptoms and akathisia were assessed with the Simpson-Angus Rating Scale and the Barnes Rating Scale for Drug-Induced Akathisia, respectively.

SPECT imaging to determine the levels of D₂ occupancy was performed with an SME 810 brain-dedicated SPECT multidetector system. The transaxial resolution of this camera is 7.6 mm full width at half maximum of a line source in air, and the axial resolution is 13.5 mm full width at half maximum. All subjects received oral potassium iodide to block thyroid uptake of free radioactive iodide. [¹²³I]IBZM (specific activity of >185 MBq/nmol; radiochemical purity of >95%) was injected intravenously at an approximate dose of 110 MBq. ¹²³I labeling of IBZM was performed by Amersham Cygne (Technical University Eindhoven, the Netherlands). SPECT image acquisition was always performed 2 hours postinjection (29). SPECT imaging was performed after 6 weeks of continuous treatment with the study medication. All scans were carried out 12 to 13 hours after the administration of the last dose of the study medication. Specifications and imaging procedures have been described elsewhere (30).

Data Analysis

Semiquantification of [¹²³I]IBZM binding was performed by placing a template of fixed regions of interest over the striatum and occipital cortex (30). Specific striatal binding was defined as striatal binding divided by occipital binding (30). All analyses were performed blind to the clinical data.

A group of nine healthy comparison subjects meeting the following criteria—no current or past psychiatric, neurological, or medical illness; no use of medication; age 17–28 years—was included to obtain baseline dopamine receptor densities. Their mean [¹²³I]IBZM binding ratio was 1.92 (SD=0.08), which was used

TABLE 1. Characteristics and 6-Week Measures of Patients With Recent-Onset Schizophrenia Randomly Assigned to Double-Blind Treatment With Either Olanzapine (7.5 mg/day) or Haloperidol (2.5 mg/day)

Medication Group and Patient	Age (years)	Schizophrenia Subtype	Number of Psychotic Episodes	Duration of Illness (months)	Medication Before Study and Dose (mg/day)	Oxazepam Dose (mg/day)	Week 6 Measure			
							Psychometric Rating			
							Subjective Well-Being Under Neuroleptics Scale ^a	Positive and Negative Syndrome Scale	Montgomery-Åsberg Depression Rating Scale	D ₂ Receptor Occupancy (%)
Olanzapine										
1	20	Disorganized	1	12	Pimozide, 4	0	154	48	2	36
2	20	Paranoid	1	15	Olanzapine, 15	200	116	69	10	43
3	23	Disorganized	1	36	Risperidone, 5	50	142	89	16	43
4	26	Undifferentiated	1	24	Haloperidol, 3	30	141	46	18	44
5	23	Disorganized	1	19	Risperidone, 3	30	202	41	0	45
6	20	Undifferentiated	1	24	Pimozide, 1	0	147	86	17	57
7	17	Paranoid	1	5	Risperidone, 5	0	204	33	0	60
8	19	Paranoid	1	9	Olanzapine, 10	0	181	39	4	64
9	22	Paranoid	1	24	Quetiapine, 200	0	142	79	28	67
10 ^b	20	Paranoid	1	4	Zuclopentixol, 12	50				
11 ^b	22	Paranoid	2	13	Haloperidol, 3	0				
12 ^b	20	Undifferentiated	1	18	Risperidone, 8	0				
Haloperidol										
1	19	Undifferentiated	1	3	Risperidone, 2	40	163	79	7	45
2	25	Undifferentiated	2	40	Pimozide, 1	0	197	76	6	58
3	18	Disorganized	1	10		0	201	84	6	61
4 ^c	17	Paranoid	1	3	Risperidone, 4	0	223	44	4	64
5	21	Disorganized	1	36		30	166	91	16	64
6	24	Paranoid	1	2	Haloperidol, 5	10	210	30	2	66
7	22	Paranoid	1	5	Risperidone, 5	0	140	53	20	71
8	19	Undifferentiated	2	18	Risperidone, 4	75	131	76	9	71
9	18	Paranoid	1	5	Risperidone, 5	30	153	45	6	71
10	21	Paranoid	1	4	Risperidone, 4	0	150	39	7	74
11	24	Paranoid	2	36	Risperidone, 8	0	129	48	4	75
12 ^b	24	Paranoid	1	12	Pimozide, 8	30				

^a Higher scores reflect better subjective experience (total score range=38–228).

^b Study dropout.

^c Female subject.

to calculate the percentage of occupancy by medication as follows: (ratio striatum/occipital region)–1/(1.92–1)×(–100)+100.

By computing the mean absolute difference between the positively and the comparative negatively formulated items of the Subjective Well-Being Under Neuroleptics Scale, we estimated the reliability of the patient's assessment with the Subjective Well-Being Under Neuroleptics Scale before further analyses were done. If the mean absolute difference was 2 or higher, the patient's assessment was considered to be not consistent, and these patients were excluded from analysis relating to subjective experience (17, 28).

Differences between groups were tested with a *t* test, and differences within patients between baseline and endpoint were tested with a paired *t* test. All tests were two-tailed.

Results

Subjects

Twenty-four patients with schizophrenia according to DSM-IV criteria were included. Subjects' characteristics, including characteristics of the illness and Subjective Well-Being Under Neuroleptics Scale total score, psychopathology ratings, and percentage of D₂ receptor occupancy at endpoint, are shown in Table 1. Characteristics of the participants (sex, diagnosis, number of episodes, duration of psychosis, and prior treatment) treated with

olanzapine did not significantly differ at baseline from the characteristics of participants treated with haloperidol.

Three patients treated with olanzapine and one patient treated with haloperidol dropped out. Reasons for dropping out were patient decision (N=2, both olanzapine) and increase of psychosis (N=2, one patient treated with haloperidol, one patient treated with olanzapine). There were no significant differences between patients who dropped out and study completers with respect to diagnosis, number of psychotic episodes, duration of psychotic symptoms, psychopathology, or subjective experience ratings.

Mean absolute difference between the positively and the comparative negatively formulated items of the Subjective Well-Being Under Neuroleptics Scale was 0.58 (SD=0.34). Only one patient (haloperidol group) had a mean absolute difference of 2 or higher (2.9). This assessment was considered to be not consistent and was excluded from analysis relating to subjective experience.

Subjective Experience and D₂ Receptor Occupancy

Mean baseline and change at endpoint scores for measures of the Subjective Well-Being Under Neuroleptics

TABLE 2. Change in Subjective Experience of Patients With Recent-Onset Schizophrenia After 6 Weeks of Double-Blind Treatment With Either Olanzapine (7.5 mg/day) or Haloperidol (2.5 mg/day)

Measure From the Subjective Well-Being Under Neuroleptics Scale ^a	Score				Analysis	
	Olanzapine Group (N=9)		Haloperidol Group (N=10)			
	Mean	SD	Mean ^b	SD	t (df=17)	p
Total scale						
Baseline	154.0	21.1	158.0	35.9	0.29	0.77
Change at endpoint	4.7	15.6	11.7**	10.2	-1.19	0.26
Emotional regulation						
Baseline	29.7	7.3	31.7	9.5	0.52	0.61
Change at endpoint	1.8	3.7	3.5**	3.2	-1.01	0.33
Self-control						
Baseline	26.0	4.5	27.1	5.7	0.46	0.65
Change at endpoint	-0.9	4.1	2.3**	1.4	-2.33	0.03
Mental functioning						
Baseline	34.1	5.0	33.5	7.2	-0.21	0.84
Change at endpoint	1.7	5.8	2.5*	3.1	-0.34	0.74
Physical functioning						
Baseline	28.7	4.6	26.7	6.1	-0.78	0.44
Change at endpoint	0.0	4.0	1.8**	1.5	-1.31	0.21
Social functioning						
Baseline	32.3	5.0	35.7	7.4	1.41	0.27
Change at endpoint	2.2	5.0	1.3	3.1	0.47	0.64

^a Higher scores reflect better subjective experience (total score range=38–228).

^b Asterisks denote significant within-treatment differences (paired t test, two-tailed).

*p<0.05. **p<0.01.

TABLE 3. Subjective Experience of Patients With Recent-Onset Schizophrenia by D₂ Receptor Occupancy Level After 6 Weeks of Double-Blind Treatment With Either Olanzapine (7.5 mg/day) or Haloperidol (2.5 mg/day)

Measure From the Subjective Well-Being Under Neuroleptics Scale ^a	Score						Analysis ^b	
	0%–59% Occupancy (N=8)		60%–70% Occupancy (N=6)		71%–100% Occupancy (N=5)			
	Mean	SD	Mean	SD	Mean	SD	t (df=9)	p
Total scale	157.8	29.1	193.5	28.7	140.6	10.8	3.9	0.004
Emotional regulation	32.4	8.6	40.3	8.2	27.0	4.1	3.3	0.009
Self-control	24.6	4.7	32.0	4.9	26.2	3.7	2.2	0.06
Mental functioning	35.5	6.8	41.5	4.4	30.0	2.5	5.2	0.001
Physical functioning	27.6	4.9	33.7	4.5	24.7	2.3	4.3	0.002
Social functioning	34.1	5.0	42.0	7.0	31.2	4.0	3.0	0.02

^a Higher scores reflect better subjective experience (total score range=38–228).

^b Difference in score between participants with a D₂ receptor occupancy level of 60%–70% and those with a level higher than 70%.

Scale did not differ significantly between participants treated with haloperidol or olanzapine except for a significant difference in the change at endpoint score for the self-control subscale in favor of haloperidol. Total score and four of the five subscale scores of the Subjective Well-Being Under Neuroleptics Scale improved significantly from baseline to endpoint in the patients treated with haloperidol (Table 2).

As seen in Table 3 and Figure 1, patients with D₂ receptor occupancy levels between 60% and 70% (N=6) had a significantly higher total score on the Subjective Well-Being Under Neuroleptics Scale than did subjects with D₂ receptor occupancy levels higher than 70% (N=5). In addition, the total score on the Subjective Well-Being Under Neuroleptics Scale for subjects with D₂ receptor occupancy levels between 60% and 70% was significantly higher when compared with that of subjects with D₂ receptor occupancy levels either lower than 60% or higher than 70% (N=13; mean=151.2, SD=24.7) (t=3.3, df=17, p=0.004). The mean scores on all the subscales of the Subjec-

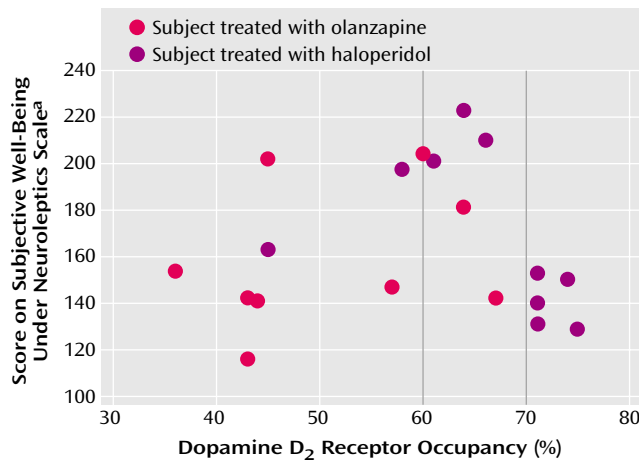
tive Well-Being Under Neuroleptics Scale were significantly higher in subjects with D₂ receptor occupancy levels between 60% to 70% than in those with D₂ receptor occupancy levels higher than 70% (Table 3).

Subjects treated with haloperidol accounted for most of the difference in scores on the Subjective Well-Being Under Neuroleptics Scale between participants with D₂ receptor occupancy levels of 60%–70% (mean=211.3, SD=11.1, N=3) and those with D₂ receptor occupancy levels of 71% or higher (mean=140.6, SD=10.8, N=5) (t=8.9, df=6, p<0.001).

The mean D₂ receptor occupancy level in patients treated with olanzapine, 7.5 mg/day, was 51.0% (SD=11.1%, range=36%–67%). This was significantly lower than the mean D₂ receptor occupancy level of 65.5% (SD=8.7%, range=45%–75%) seen in patients treated with haloperidol, 2.5 mg/day (t=3.3, df=18, p=0.004) (Figure 2).

D₂ receptor occupancy level was not related to any baseline variable (age, weight, nicotine use, coffee use, or severity of illness).

FIGURE 1. Relationship Between Subjective Well-Being and D₂ Receptor Occupancy Level in Patients With Recent-Onset Schizophrenia After 6 Weeks of Double-Blind Treatment With Either Olanzapine (7.5 mg/day) or Haloperidol (2.5 mg/day)



^a Higher scores reflect better subjective experience (total score range=38–228).

Psychopathology and Extrapyramidal Side Effects

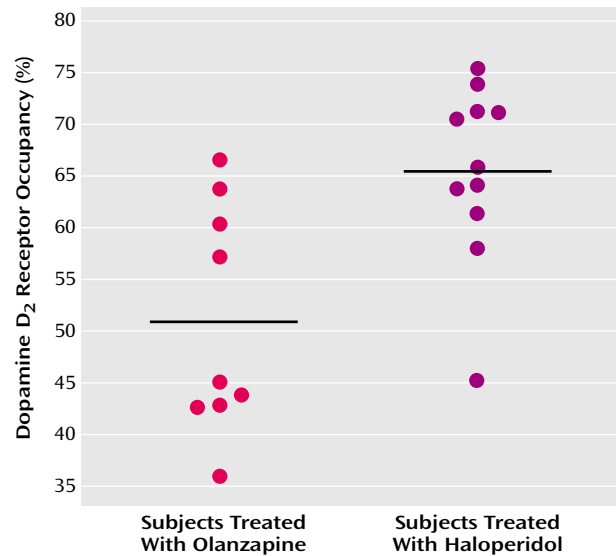
Significant improvement in CGI scores was seen in the patients treated with olanzapine (mean change at endpoint=−1.3 [SD=1.0]; $t=3.42$, $df=7$, $p<0.05$) and in the patients treated with haloperidol (mean change at endpoint=−0.8 [SD=0.9]; $t=?$, $df=10$, $p<0.05$). For the patients treated with olanzapine and those treated with haloperidol, non-significant improvement was seen for total scores on the Positive and Negative Syndrome Scale (mean change at endpoint=−7.2 [SD=31.9] and −11.4 [SD=19.5], respectively) and the Montgomery-Åsberg Depression Rating Scale (mean change at endpoint=−2.8 [SD=12.1] and −1.2 [SD=3.6]). No significant differences in mean baseline (data not shown) and change at endpoint scores were found between participants treated with haloperidol and olanzapine.

We found no relationship between level of D₂ receptor occupancy and response defined as difference in Clinical Global Impression, Positive and Negative Syndrome Scale, and Montgomery-Åsberg Depression Rating Scale scores between baseline and endpoint.

No relationship was found at endpoint between D₂ receptor occupancy level and Positive and Negative Syndrome Scale total or subscale scores or Montgomery-Åsberg Depression Rating Scale scores.

At baseline, participants treated with haloperidol experienced more akathisia (mean=0.6, SD=0.8) than participants treated with olanzapine (mean=0.0, SD=0.0) ($t=2.35$, $df=18$, $p<0.05$) as measured with the Barnes Akathisia Scale. Change at endpoint did not differ significantly between groups. Within the haloperidol group, mean score on the Simpson-Angus Scale improved significantly

FIGURE 2. D₂ Receptor Occupancy Levels in Patients With Recent-Onset Schizophrenia After 6 Weeks of Double-Blind Treatment With Either Olanzapine (7.5 mg/day) or Haloperidol (2.5 mg/day)



(mean change at endpoint=−3.9, SD=5.0) ($t=2.47$, $df=9$, $p<0.05$).

At endpoint, akathisia and parkinsonism were generally absent. No relationship between the D₂ receptor occupancy percentage and Barnes Akathisia Scale scores or Simpson-Angus Scale scores was found at endpoint.

Discussion

The results of this study offer evidence that D₂ receptor occupancy between 60% and 70% is optimal for subjective experience of patients with recent-onset schizophrenia. Exceeding a level of 70% D₂ receptor occupancy may substantially increase the risk of inducing worse subjective experience and noncompliance and therefore psychotic relapse.

The very low incidence and severity of extrapyramidal side effects we found is in line with the D₂ receptor occupancy threshold of 78% for development of extrapyramidal side effects. We were not able to replicate the relationship between D₂ receptor occupancy and response as found by Kapur et al. (10). None of our patients had D₂ receptor occupancy levels that exceeded 75%, whereas five of the 10 patients with CGI scores that were much or very much improved in the study of Kapur et al. had D₂ receptor occupancy levels that exceeded 75%. This leaves clinicians with an almost insurmountable problem: the level of D₂ receptor occupancy needed for response in some patients exceeds the level above which the risk of negative influence on subjective experience is probably high. However, since the duration of treatment in the study by Kapur et al. (10) was only 2 weeks, a D₂ receptor occupancy level lower than 75% for a longer period of time may result in response in most patients. Moreover, most of our patients

had been treated with antipsychotic medication before study entry, thereby increasing the risk of a higher percentage of patients with treatment resistance than in a neuroleptic-naïve population. This may also explain why we could not replicate the relationship between D₂ receptor occupancy and response.

We found a lower mean D₂ receptor occupancy (65.5%) in patients treated with haloperidol, 2.5 mg/day, than did Kapur et al. (10), whose nine first-episode patients also received haloperidol, 2.5 mg/day (mean D₂ receptor occupancy=75%). This difference could reflect the need for treatment with very low doses for neuroleptic-naïve patients compared with patients who have been treated with antipsychotic medication before. As far as we know, it is not clear when the need for higher doses emerges during treatment with antipsychotic medication.

The substantial interindividual variation in D₂ receptor occupancy at fixed amounts of low-dose haloperidol and olanzapine in this homogeneous group of subjects was in concordance with the wide interindividual variation at a given dose of haloperidol found in other studies (7, 10).

Mean D₂ receptor occupancy in patients treated with olanzapine, 7.5 mg/day, was significantly lower than mean D₂ occupancy reached during treatment with haloperidol, 2.5 mg/day. The mean D₂ occupancy found with olanzapine, 7.5 mg/day, is in line with the saturation hyperbola as earlier described (23). In a study on the D₂ receptor occupancy of olanzapine, more interindividual variation seemed to occur in patients receiving 5 mg/day of olanzapine than in patients receiving doses of 10 mg/day or higher (23). In our study, more than half of the patients treated with olanzapine, 7.5 mg/day, reached D₂ receptor occupancy of 45% or less; however, one-third of these patients showed an occupancy of 60% or more.

Olanzapine, 7.5 mg/day, did not show superior subjective response compared with haloperidol, 2.5 mg/day, in patients with recent-onset schizophrenia. In fact, subjective experience improved significantly only during treatment with haloperidol. This is an unexpected finding given the advantages in subjective experience found during treatment with olanzapine in former studies. Inordinately high levels of D₂ receptor occupancy in the typical comparison group have confounded these studies. However, our study may be biased by the relatively low D₂ receptor occupancy associated with the treatment of olanzapine, 7.5 mg/day. We therefore cannot rule out the possibility that olanzapine in a dose that gives rise to D₂ receptor occupancy beyond 70% may still result in superior subjective well-being. The decline in subjective well-being with an occupancy of striatal D₂ receptors above 70% may be an issue only relevant for haloperidol. However, future studies are needed to test this hypothesis.

Fast dissociation from the D₂ receptor could make an antipsychotic medication more accommodating of physiological dopamine transmission, permitting antipsychotic effect without major side effects (25). This proposed mechanism

could also account for superior subjective experience associated with atypical antipsychotic drugs. Since we found no evidence for superior subjective experience associated with low-dose olanzapine compared with low-dose haloperidol, we suppose that besides faster dissociation, the level of D₂ occupancy is also important for the influence of antipsychotic drugs on subjective experience. Moreover, subjective experience is probably influenced not only by effects on modulation of the D₂ neurotransmission but effects on receptors other than D₂ may also account for worse subjective experience. Probably an ideal antipsychotic medication binds selectively to the D₂ receptor and dissociates relatively fast from it, without causing enduring occupancy beyond about 70%.

Our study has several limitations. First, mesolimbic D₂ receptors might be more relevant to subjective experience than striatal D₂ receptors. Since there are no indications for differences in striatal and extrastriatal D₂ occupancy in patients treated with haloperidol, we think that striatal occupancy is a reasonable surrogate of mesolimbic D₂ occupancy, at least in the case of haloperidol (31, 32). Second, most of the patients included used antipsychotic medication before study entry, probably altering their D₂ binding capacity. We think that the study duration of 6 weeks makes confounding effects on subjective experience measures caused by former medication less probable. Third, one-half of the patients used oxazepam as adjunctive medication. However, occupancy in a PET study of lorazepam has been shown to have no influence on striatal [¹¹C]raclopride binding (33). Fourth, the 7.5 mg/day dose of olanzapine was too low for most (not all) patients with recent-onset schizophrenia previously treated with antipsychotic medication. Comparison of haloperidol, 2.5 mg/day, with olanzapine, 10 mg/day, might give ideal D₂ occupancy matching. Future comparison of subjective experience of typical and atypical antipsychotic medication in doses that lead to the same range of D₂ receptor occupancy is needed. Fifth, only one out of 24 subjects was female. Finally, in the present study plasma levels of study medication were not measured. However, compliance with study medication was guaranteed, since nursing staff supervised intake of medication.

In summary, we found evidence that a level of D₂ receptor occupancy between 60% and 70% is optimal for subjective experience of patients with recent-onset schizophrenia. We found substantial interindividual variation in D₂ receptor occupancy at fixed amounts of low-dose haloperidol and olanzapine. Olanzapine, 7.5 mg/day, showed no superior subjective response over haloperidol, 2.5 mg/day. From the perspective of subjective experience of patients, haloperidol needs to be individually titrated in the very low dose range (probably 1.5–3 mg/day) to reach optimal occupancy, and olanzapine needs to be dosed higher than 7.5 mg/day for most patients with recent-onset schizophrenia previously treated with antipsychotic medication.

Received Sept. 24, 2001; revision received June 5, 2002; accepted Aug. 1, 2002. From the Academic Medical Center, University of Amsterdam Department of Psychiatry. Address reprint requests to Dr. de Haan, Academic Medical Center, University of Amsterdam Department of Psychiatry, Postbox 22700, 1100 DE Amsterdam, the Netherlands; l.dehaan@amc.uva.nl (e-mail).

Supported by grant 28-1241-2 from the Dutch Health Research and Development Council.

References

- Haase HJ: Extrapyrimal modification of fine movements: a "conditio sine qua non" of the fundamental neuroleptic action of neuroleptic drugs, in *Système Extrapyrimal et Neuroleptiques*. Edited by Bordeleau JM. Montreal, Editions Psychiatriques, 1961, pp 329–353
- McEvoy JP, Hogarty GE, Steingard S: Optimal dose of the neuroleptic in acute schizophrenia. *Arch Gen Psychiatry* 1991; 48: 739–745
- Bollini P, Pampallona S, Orza MJ, Adams ME, Chalmers TC: Antipsychotic drugs: is more worse? a meta-analysis of the published randomised control trials. *Psychol Med* 1994; 24:307–316
- Farde L, Hall H, Ehrin E, Sedvall G: Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. *Science* 1986; 231:258–261
- Wolkin A, Brodie JD, Barouche F, Rotrosen J, Wolf AP, Smith M, Fowler J, Cooper TB: Dopamine receptor occupancy and plasma haloperidol levels. *Arch Gen Psychiatry* 1989; 46:482–484
- Wolkin A, Barouche F, Wolf AP, Rotrosen J, Fowler JS, Shiue CY, Cooper TB, Brodie JD: Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. *Am J Psychiatry* 1989; 146:905–908
- Kapur S, Remington G, Jones C, Wilson A, DaSilva J, Houle S, Zipursky R: High levels of dopamine D₂ receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry* 1996; 153:948–950
- Nordström AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, Uppfeldt G: Central D₂ dopamine receptor occupancy in relation to antipsychotic drug effects—a double-blind PET study of schizophrenic patients. *Biol Psychiatry* 1993; 33:227–235
- Nyberg S, Farde L, Halldin C, Dahl M-L, Bertilsson L: D₂ dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. *Am J Psychiatry* 1995; 152:173–178
- Kapur SJ, Zipursky R, Jones C, Remington G, Houle S: Relationship between dopamine D₂ occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 2000; 157:514–520
- Koob GF: Drug of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci* 1992; 13:177–184
- de Haan L, Lavalaye J, Linszen D, Dingemans PMAJ, Booij J: Subjective experience and striatal dopamine D₂ receptor occupancy in patients with schizophrenia stabilized by olanzapine or risperidone. *Am J Psychiatry* 2000; 157:1019–1020
- Sherer MA, Kumor KM, Jaffe JH: Effects of intravenous cocaine are partially attenuated by haloperidol. *Psychiatry Res* 1989; 27:117–125
- Bressan RA, Costa DC, Jones HJ, Ell PJ, Kerwin RW, Pilowsky LS: Striatal D₂ blockade and depression in schizophrenia—SPET findings (abstract). *Biol Psychiatry* 2000; 47:128S
- Bressan RA, Jones MH, Ell PJ, Pilowsky LS: Dopamine D₂ receptor blockade in schizophrenia (letter). *Am J Psychiatry* 2001; 158:971–972
- Volkow ND, Wang G-J, Fowler JS, Logan J, Gatley SJ, Gifford A, Hitzemann R, Ding Y-S, Pappas N: Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D₂ receptor levels. *Am J Psychiatry* 1999; 156:1440–1443
- Naber D: A self-rating to measure subjective effects of neuroleptic drugs: relationships to objective psychopathology, quality of life, compliance and other clinical variables. *Int Clin Psychopharmacol* 1995; 10:133–138
- van Putten T, May PRA, Marder SR: Subjective response to antipsychotic drugs. *Arch Gen Psychiatry* 1981; 38:187–190
- Hogan TP, Awad AG, Eastwood R: A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med* 1983; 13:177–183
- Buis W: Patients' opinions concerning side effects of depot neuroleptics (letter). *Am J Psychiatry* 1992; 149:844–845
- Naber D, Moritz SM, Lambert M, Pajonk F, Holzbach R, Mass R, Andersen B, Frank P, Rudger H, Reinhard M, Burghard A: Improvement of schizophrenic patients, subjective well-being under atypical antipsychotic drugs. *Schizophr Res* 2001; 50:79–88
- Franz M, Lis S, Plüddemann K, Gallhofer B: Conventional versus atypical neuroleptics: subjective quality of life in schizophrenic patients. *Br J Psychiatry* 1997; 170:422–425
- Kapur S, Zipursky RB, Remington G: Clinical and theoretical implications of 5-HT₂ and D₂ receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 1999; 156:286–293
- Spitzer RL, Williams JBW: Classification of mental disorders, in *Comprehensive Textbook of Psychiatry*, 4th ed. Edited by Kaplan HJ, Sadock BJ. Baltimore, Williams & Wilkins, 1985, pp 1035–1071
- Kapur S, Seeman P: Does fast dissociation from the dopamine D₂ receptor explain the action of atypical antipsychotics? a new hypothesis. *Am J Psychiatry* 2001; 158:360–369
- Tauscher J, Küfferle B, Asenbaum S, Fischer P, Pezawas L, Barbas C, Tauscher-Wisniewski S, Brucke T, Kasper S: In vivo 123I IBZM SPECT imaging of striatal dopamine-2 receptor occupancy in schizophrenic patients treated with olanzapine in comparison to clozapine and haloperidol. *Psychopharmacology (Berl)* 1999; 141:175–181
- Nordström AL, Nyberg S, Olsson H, Farde L: Positron emission tomography finding of a high striatal D₂ receptor occupancy in olanzapine-treated patients. *Arch Gen Psychiatry* 1998; 55: 283–284
- de Haan L, Weisfelt M, Dingemans PMAJ, Linszen DH, Wouters L: Psychometric properties of the Subjective Well-Being Under Neuroleptics Scale (SWN) and the Subjective Deficit Syndrome Scale (SDSS). *Psychopharmacology (Berl)* 2002; 162:24–28
- Verhoeff NP, Brücke T, Podreka I, Bobeldijk M, Angelberger P, Van Royen EA: Dynamic SPECT in two healthy volunteers to determine the optimal time for in vivo D₂ dopamine receptor imaging with 123I-IBZM using the rotating gamma camera. *Nucl Med Commun* 1991; 12:687–697
- Verhoeff NP, Kapucu O, Sokole-Busemann E, Van Royen EA, Janssen AG: Estimation of dopamine D₂ receptor binding potential in striatum with iodine-123-IBZM SPECT: technical and interobserver variability. *J Nucl Med* 1993; 34:2076–2084
- Farde L, Suhara T, Nyberg S, Karlsson P, Nakashima Y, Hietala J, Halldin C: A PET-study of [11C]FLB 457 binding to extrastriatal D₂-dopamine receptors in healthy subjects and antipsychotic drug-treated patients. *Psychopharmacology (Berl)* 1997; 133: 396–404
- Hietala J, Vilkmann H, Syvälahti E, Nägren K: Extrastriatal and striatal dopamine receptor occupancy by haloperidol and clozapine measured with PET, in *Abstracts of the 21st CINCP Congress*. Glasgow, UK, Collegium Internationale Neuro-Psychopharmacologicum, 1998, SW0104
- Hietala J, Kuoppamäki M, Nägren K, Lehtikoinen P, Syvälahti E: Effects of lorazepam administration on striatal dopamine D₂ receptor binding characteristics in man—a positron emission tomography study. *Psychopharmacology (Berl)* 1997; 132:361–365