Emotional Experience and Estimates of D_2 Receptor Occupancy in Psychotic Patients Treated With Haloperidol, Risperidone, or Olanzapine: An Experience Sampling Study

Johan Lataster, MSc; Jim van Os, MD, PhD; Lieuwe de Haan, MD, PhD; Viviane Thewissen, PhD; Maarten Bak, MD, PhD; Tineke Lataster, PhD; Mariëlle Lardinois, PhD; Philippe A. E. G. Delespaul, PhD; and Inez Myin-Germeys, PhD

ABSTRACT

Objective: Blockade of dopamine D_2 receptors is thought to mediate the therapeutic effects of antipsychotic medication but may also induce social indifference. As antipsychotic drugs differ in D_2 receptor binding, "tight" and "loose" binding drugs may be hypothesized to differentially affect emotional experience. The present study investigates the differential effects of relatively tight versus looser binding drugs on the experience of emotions in the realm of daily life.

Method: We assessed positive and negative affect in the daily life of 109 patients with a *DSM-IV* diagnosis of psychotic disorder who were currently taking antipsychotic medication by using the experience sampling method (a structured diary technique). Antipsychotic medication was classified as loose (olanzapine; n = 35) or tight (haloperidol, risperidone; n = 74) binding, based on the drug's dissociation constants at the D_2 receptor. The study was conducted from 2007 to 2008.

Results: Multilevel analyses showed a significant interaction between binding group (loose vs tight) and D_2 receptor occupancy estimates with regard to the experience of positive ($P = .008$) and negative ($P = .019$) affect. For tight-binding–agent users, a significant association was found between D_2 receptor binding estimates and both positive affect ($P = .040$) and negative affect ($P = .0001$) in the flow of daily life, with increasing levels of estimated D_2 receptor occupancy being associated with decreased feelings of positive affect and increased feelings of negative affect. For loose-binding–agent users, no such association was apparent. These associations were only partly mediated by clinical symptoms.

Conclusions: These findings add ecological validity to previous laboratory findings showing an association between D_2 receptor occupancy and emotional experience.

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Corresponding author: *Inez Myin-Germeys, PhD, Department of Psychiatry and Neuropsychology, Maastricht University, PO Box 616 (VIJV), 6200MD Maastricht, The Netherlands (i.germeys@maastrichtuniversity.nl).*

Antipsychotic medication reduces dopaminergic neurotransmission and reduces positive symptoms in patients diagnosed with schizophrenia.[1–3] Given the fact that the dopaminergic system may mediate the experience of motivational salience or reward,[4,5] antipsychotic medication may act by making abnormal perceptions and delusional beliefs become less meaningful and lose part of their intensity and presence.[6] There is evidence, however, that by doing so they may also induce motivational indifference and block emotional experience.[7] Despite the apparent link between dopamine blockade and motivational indifference, symptom reduction and occurrence of extrapyramidal side effects have long been the main outcome measures in medication studies.[8] However, the occurrence of emotional impairment may be a more subtle yet more important side effect of antipsychotic medication, as it already occurs at relatively low levels of dopamine receptor blockade.[9]

Emotional experience has been shown to change in response to antipsychotic treatment.[10–12] More specifically, experience of emotions has been related to occupancy of the dopamine D_2 receptor, with high levels of D_2 receptor occupancy being associated with feelings of dysphoria and decreased feelings of safety and self-confidence,[13,14] independent of overall symptom severity[14] or extrapyramidal symptoms (EPS).[13,14] Similarly, prolonged dopamine depletion has been shown to result in negative mood states.[15] However, the relationship between D_2 occupancy and emotional experience may not be linear.[9] For example, lower D_2 occupancy levels may be related to reduced motivational tone due to the presence of psychotic symptoms, whereas high D_2 receptor blockade may induce motivational indifference due to blockade of emotional experience associated with natural rewards.

Research in the area has been conducted by assessing emotional experience ("subjective well-being") using medication-related cross-sectional questionnaires in semiexperimental environments. While productive, these studies nevertheless lack ecological validity, as emotional experiences occurring in the flow of daily life are assessed retrospectively and globally using cross-sectional instruments. Assessing emotional states in the reality of daily life would allow examination of more subtle changes in emotional experience. This may be crucially important given the impact of subjective well-being on medication compliance and treatment outcome.[16,17] The current study therefore aimed to investigate the association between D_2 receptor occupancy and experience of emotions in daily life reality by using the experience sampling method (ESM), a fine-grained momentary assessment technique, to collect emotional experiences in the flow of daily life.[18,19]

Furthermore, although all antipsychotic drugs display some degree of blockade of the D_2 receptor, the specific mechanism of occupancy is determined by the chemical profile of the individual agent.[20] Antipsychotic agents differ in how strongly they compete with dopamine for occupancy of the D_2 receptor. Some agents, such as haloperidol and risperidone, bind more tightly to the D_2 receptor than dopamine itself. Others, however, such as olanzapine and clozapine, display a more loose or "rapid offset" binding

profile, making them more easily displaceable by endogenous dopamine.[21] It is attractive to hypothesize that these differences in binding potential could result in differential effects on experience of reward. De Haan and colleagues[9] described an overall effect of D_2 occupancy on emotional experience in haloperidol and olanzapine users. However, Garcia-Cabeza and coworkers[22] found treatment with the more tight-binding agents haloperidol and risperidone to be associated with more negative feelings than treatment with the more loose-binding agent olanzapine. Thus, although closely linked, the overall amount of D_2 occupancy and the qualitative aspects involved in the process of dopaminergic antagonism need to be disentangled with regard to subjectively experienced medication effects impacting on the experience of emotions.

The present study thus investigated the effect of medication use on emotional experience quantified as positive affect and negative affect in the realm of daily life. In addition, the differential effects of relatively tight- and loose-binding drugs on experience of emotions were investigated. The study was naturalistic, meaning that subjects were taking antipsychotic medication as prescribed by their clinician. For the more tight-binding drugs, a first-generation antipsychotic—haloperidol—and a second-generation antipsychotic—risperidone—were included, and compared with the looser binding second-generation antipsychotic olanzapine.

METHOD

Subjects

The sample consisted of 119 patients with a lifetime diagnosis of nonaffective psychosis. Inclusion criteria were (1) age 18–65 years; (2) sufficient command of the Dutch language to understand instructions and informed consent; (3) a lifetime diagnosis of nonaffective psychosis; and (4) current use of haloperidol, risperidone, or olanzapine. Exclusion criteria were (1) endocrine, cardiovascular, or brain disease; (2) weekly use of illicit drugs; and (3) use of alcohol in excess of 5 standard units per day. Patients were recruited through inpatient and outpatient mental health facilities in Maastricht (The Netherlands) as well as through patient associations in the southern part of The Netherlands. The study was conducted from 2007 to 2008.

Diagnostic inclusion of patients was based on *DSM-IV* diagnoses,[23] generated with the OPCRIT computer program.[24] Participants included patients with a diagnosis of schizophrenia, delusional disorder, induced psychotic disorder, brief psychotic disorder, and psychotic disorder not otherwise specified. This study was approved by the local medical ethics committee. After complete description of the study to the participants, signed informed consent was obtained.

Experience Sampling Method

The ESM is a within-day momentary self-assessment technique developed to provide measures of the frequency and patterns of mental processes in everyday life situations.[18,19]

Participants received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. Ten times a day on 6 consecutive days, the watch emitted a signal (beep) at unpredictable moments between 7:30 AM and 10:30 PM. After each beep, subjects were asked to stop their activity and fill out the ESM self-assessment forms previously handed out to them, collecting reports of perceptions, thoughts, mood, current context (activity, persons present, location) and appraisals of the current situation. All self-assessment items were rated on 7-point Likert scales. Subjects were asked to complete their reports immediately after the beep, thus minimizing memory distortions, and to record the time at which they completed the form. In order to know whether the subjects had completed the form within 15 minutes after the beep, the time at which subjects indicated they completed the report was compared to the actual time of the beep. All reports completed more than 15 minutes after the signal were excluded from the analysis. Previous work has shown that reports completed after this interval are less reliable and consequently less valid.[19] For the same reason, subjects with less than 20 valid reports were also excluded from the analysis.

Experience of Emotions

Emotional experience was assessed with 4 positive affect items and 6 negative affect items rated on 7-point Likert scales (rating from "not at all" [= 1] to "very" [= 7]), derived from the ESM booklets as described above. Mean scores on the items "I feel cheerful," "I feel relaxed," "I feel satisfied," and "Overall, I am feeling well" (Cronbach $\alpha = .85$) constituted the positive affect scale. The negative affect scale consisted of mean scores on the items "I feel insecure," "I feel lonely," "I feel anxious," "I feel down," "I feel angry," and "I feel guilty" (Cronbach $\alpha = .83$).

Symptomatology

Momentary psychotic symptomatology was assessed with 2 perception and 2 thought items rated on 7-point Likert scales (rating from "not at all" [= 1] to "very" [= 7]) derived from the ESM booklets. Mean scores on the items "I hear voices" and "I see phenomena" constituted the hallucinations scale (Cronbach $\alpha = .74$), while mean scores on the items "I feel suspicious" and "I feel unreal" constituted the delusions scale (Cronbach $\alpha = .66$).

Overall symptom severity during the ESM-week was assessed once with the Brief Psychiatric Rating Scale (BPRS),[25] a semistructured interview. The BPRS consists of 24 pathology items scored on a 7-point severity scale (ranging from "not present" to "extremely severe"). Scoring was conducted by trained raters. Mean values of the 24 pathology item scores were used as an indicator of severity of symptomatology, with higher scores representing more severe symptoms. In addition, according to Velligan et al,[26] BPRS depression and BPRS psychosis subscale scores were calculated for each subject, consisting of the mean scores on BPRS items that have been shown to cluster together in a depression/anxiety factor (somatic concern, anxiety,

Table 1. Sociodemographic Characteristics of the Sample and Concomitant Psychotropic Medication Use

Characteristic	Tight-Binding–Agent Haloperidol Users	Tight-Binding–Agent Risperidone Users	Loose-Binding–Agent Olanzapine Users
Age, mean (SD), range, y	37.5 (8.1), 20–60	31.7 (8.6), 18–52	33.7 (11.8), 19–63
Gender, n			
Male	27	23	29
Female	12	12	6
Education, %			
Elementary school	21	33	16
Secondary school	16	52	18
Higher education	63	15	66
Marital status, %			
Married or cohabitating	22	14	13
Divorced	19	0	11
Never married	59	86	76
Inpatient status, %	39	49	46
Outpatient status, %	61	51	54
Work situation, %			
Household	5	3	0
School/education	0	6	3
Regular job	7	3	3
Ill > 3 mo	2	6	6
Pensioner	0	0	3
Unfit for work	59	60	66
Unemployed	10	17	11
Sheltered work	17	5	8
Medication type, n			
Depot	16	1	1
Oral	23	34	34
Concomitant psychotropic medication, n			
Antidepressants	0	2	2
Mood stabilizers	0	0	1
Antiparkinson medication	6	4	1
Anxiolytics	0	3	3
Tranquilizers	0	3	2
Antimigraine medication	1	0	0
Total, %	18	34	26

depression, suicidality, guilt, hostility, and suspiciousness) and psychosis factor (grandiosity, suspiciousness, hallucinations, unusual thought, bizarre behavior, conceptual disorganization), respectively.

Medication

Before the start of the ESM, detailed medication information was collected (medication name and daily dosage). Depot doses were recalculated into oral daily dose values.[27]

D_2 receptor occupancy. No in vivo receptor occupancy measures were obtained, but D_2 receptor occupancy levels were estimated theoretically by fitting hyperbolic functions to dose-related D_2 occupancy data from previously performed medication studies (see eAppendix). These functions were then applied to individual subject medication data extracted from the ESM medication forms in order to theoretically predict occupancy estimates for each subject.

Binding potential. Antipsychotic agents were classified as having either a "tighter" or a "looser" binding pattern (hereafter called tight- and loose-binding agents), based on their dissociation (or inhibition) constant K at the D_2 receptor, expressed in molar (M) units.[20] Following Seeman et al,[20] we classified drugs with dissociation constants higher than 1.5 nM, which bind more loosely to the D_2 receptor than dopamine, as loose binding ($K > 1.5$ nM; olanzapine), whereas agents with dissociation constants lower than 1.5 nM, which bind more tightly to the D_2 receptor than dopamine, were classified as tight binding ($K < 1.5$ nM; haloperidol and risperidone).[20]

Data Analysis/Statistics

Since ESM data are hierarchical in nature (multiple observations [level 1] nested within subjects [level 2]), hierarchical linear models were used, taking into account that residuals are not independent, given that observations from the same subject are more similar than observations from different subjects.[28] All analyses were conducted with the xtreg procedure in STATA.[29]

Multilevel linear regression analyses were conducted with binding group (tight, loose), D_2 receptor occupancy estimates as well as their interaction as independent variable, and negative affect and positive affect as dependent variables, in 2 separate models. Stratified analyses were conducted for the loose- and the tight-binding group. In order to clarify the effect size in the stratified analyses and due to skewness of the estimated D_2 receptor occupancy distribution, we defined a 3-level dopamine D_2 receptor occupancy estimate variable (low, middle, high) for both the loose- and tight-binding group, based on the tertile scores. Sex and age were added as covariates. Concomitant use of any anxiolytic, antidepressant, mood-stabilizing, tranquilizing, or antiparkinsonian medication was also added as dichotomous covariate due to possible confounding effects on emotional well-being.

Since emotional experience may be related to symptom severity and since medication dosage (ie, D_2 receptor occupancy) may also be associated with symptom severity, we repeated the analysis adding momentary hallucinations, momentary delusions, and mean severity of psychopathology (based on the BPRS score) as possible confounders.

RESULTS

Subjects

Ten patients were excluded due to incomplete reports or incomplete medication data. The remaining group of 109 patients consisted of 79 men and 30 women and was composed of 39 haloperidol users, 35 olanzapine users, and 35 risperidone users.

Table 2. Mean (SD) Values and *t* Test Statistics of Psychopathology, Symptoms, and Independent and Dependent Variables for Tight-Binding–Agent Users and Loose-Binding–Agent Users

	Tight-Binding–Agent Users (haloperidol and risperidone), mean (SD), n = 74	Loose-Binding–Agent Users (olanzapine), mean (SD), n = 35	t_{107}	*P*
Psychopathology				
BPRS total[a]	1.8 (0.5)	1.9 (0.5)	−0.92	.192
BPRS depression[b]	2.3 (0.1)	2.6 (0.2)	−1.26	.106
BPRS psychosis[c]	1.8 (0.1)	2.0 (0.1)	−1.26	.106
Symptoms				
Momentary hallucinations[d]	1.9 (1.5)	1.9 (1.3)	−0.28	.389
Momentary delusions[d]	2.2 (1.4)	2.1 (1.0)	0.33	.369
Independent variable				
D_2 occupancy (group average)	72.0 (16.2)	61.7 (14.7)	3.19	.002
Dependent variables				
Positive affect[d]	4.6 (1.2)	4.5 (1.0)	0.38	.369
Negative affect[d]	2.0 (1.1)	2.1 (0.9)	−0.68	.271

[a]Group average of the mean score on all 24 BPRS items.
[b]Group average of the mean score on the items that form the BPRS depression scale.
[c]Group average of the mean score on the items that form the BPRS psychosis scale.
[d]For each subject, a mean was calculated over all reports, and the mean per subject was additionally aggregated over the group to obtain the group mean (SD).
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

Sample Characteristics

Sociodemographic characteristics and mean scores on independent, dependent, and psychopathology variables are shown in Table 1 and Table 2, respectively.

Haloperidol users were significantly older than risperidone and olanzapine users ($t = 2.4$, $P = .008$). Mean D_2 occupancy estimates were higher in tight-binding-agent users compared to loose-binding-agent users (72% versus 62%, respectively). Mean scores on BPRS, BPRS subscales, momentary symptoms, positive affect, and negative affect were similar between tight-binding agent users and loose-binding-agent users. Information on concomitant psychotropic medication is shown in Table 1.

Effect of Binding Tightness on the Association Between D_2 Occupancy and Emotional Experience

Multilevel linear regression analysis with only age and sex as covariates showed no main effects of D_2 receptor occupancy on negative affect ($\beta = .01$ [SE = .008], $P = .074$) or positive affect ($\beta = -.007$ [SE = .009], $P = .428$). However, a significant interaction effect was found between binding group (tight versus loose) and D_2 receptor occupancy in the model of both positive affect ($\beta = .05$ [SE = .02], $P = .008$) and negative affect ($\beta = -.04$ [SE = .02], $P = .019$), indicating a differential association between D_2 receptor occupancy and emotional experience in the loose- versus tight-binding group.

After controlling for momentary hallucinations, we found that the effect remained significant in the models predicting positive affect and negative affect ($\beta = .05$ [SE = .02], $P = .014$, and $\beta = -.04$ [SE = .02], $P = .017$, respectively). When controlling for momentary delusions, however, we found that the effect disappeared in both models: positive affect, $\beta = .03$ (SE = .02), $P = .106$; negative affect, $\beta = -.02$ (SE = .01), $P = .183$. After controlling for overall BPRS psychopathology, we found that the effect remained significant in the model predicting positive affect ($\beta = .04$ [SE = .02], $P = .050$) but lost significance in the model predicting negative affect ($\beta = -.02$ [SE = .02], $P = .197$).

In order to clarify the interaction, stratified analyses were conducted for the tight- versus loose-binding group. For both binding groups, D_2 receptor occupancy was divided into 3 based on the tertiles (1 = lowest 33⅓%, 2 = middle 33⅓%, 3 = highest 33⅓%).

Tight-Binding Agents and Their Influence on Emotional Experience

For the tight-binding group, a significant effect was found in D_2 receptor binding estimates on positive affect ($\chi^2_2 = 6.42$, $P = .040$), with age, sex, and concomitant medication use as covariates. There was a clear decrease in positive affect in the middle group (D_2 occupancy range, 68%–81%) and an even larger decrease in the group with the highest D_2 receptor occupancy (D_2 occupancy > 81%) (Table 3; Figure 1). This association, however, failed to reach significance when we additionally controlled for momentary hallucinations ($\chi^2_2 = 4.19$, $P = .123$), momentary delusions ($\chi^2_2 = 4.26$, $P = .119$), or overall BPRS psychopathology ($\chi^2_2 = 3.96$, $P = .138$) (Table 3). This was mainly due to the comparison between the highest and the lowest tertile, for which the effect lost significance, whereas the difference in positive affect between the middle and low tertile remained significant (Table 3).

D_2 occupancy was, in addition, significantly related to negative affect ($\chi^2_2 = 29.48$, $P = .0001$), with a significant increase in negative affect in the group with the highest D_2 receptor occupancy (Table 3; Figure 1), when we controlled for age, sex and concomitant medication use. The association remained large and significant after inclusion of momentary hallucinations ($\chi^2_2 = 24.11$, $P = .00001$), momentary delusions ($\chi^2_2 = 17.91$, $P = .0001$), or overall BPRS psychopathology ($\chi^2_2 = 14.83$, $P = .0006$) in the analysis (Table 3).

Loose-Binding Agents and Their Influence on Emotional Experience

No main effect of D_2 occupancy on positive affect nor negative affect was found in the loose-binding group (positive affect: $\chi^2_2 = 1.64$, $P = .439$; negative affect: $\chi^2_2 = 0.71$, $P = .701$; covariates age, sex, and concomitant medication use) (Table 3). These results did not reach significance after controlling for momentary hallucinations, momentary delusions, or overall BPRS psychopathology.

DISCUSSION

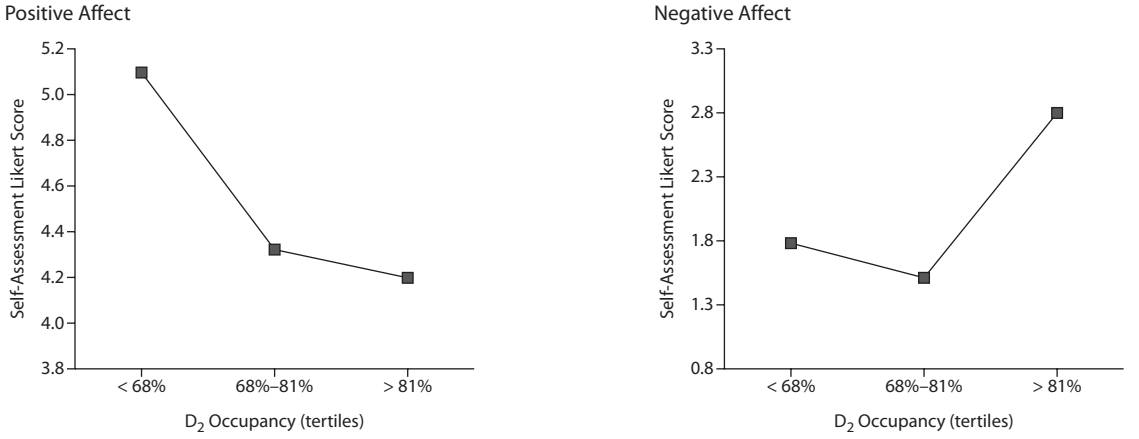
The results of this study indicate that estimated dopamine D_2 receptor occupancy may be associated with emotional

Table 3. Effect Sizes of D_2 Occupancy on Positive and Negative Affect, Displayed Separately for Tight- and Loose-Binding–Agent Users[a]

		Positive Affect After Correction				Negative Affect After Correction		
D_2 Receptor Occupancy	Positive Affect	Momentary Hallucinations	Momentary Delusions	BPRS[b]	Negative Affect	Momentary Hallucinations	Momentary Delusions	BPRS[b]
Tight-binding–agent users[c]								
Tertile 2 (68%–81%) vs tertile 1 (<68%)	–0.64†	–0.59*	–0.62†	–0.58†	–0.19	–0.24	–0.20	–0.24
Tertile 3 (>81%) vs tertile 1 (<68%)	–0.81†	–0.55	–0.30	–0.33	1.18‡	0.81‡	0.57†	0.66‡
Loose-binding–agent users[c]								
Tertile 2 (67%–74%) vs tertile 1 (<67%)	0.20	0.20	0.16	0.15	0.24	0.21	0.28	0.33
Tertile 3 (>74%) vs tertile 1 (<67%)	0.54	0.65	0.35	0.58	–0.05	–0.23	0.20	–0.13

[a]All analyses were corrected for age, sex, and concomitant medication use.
[b]Corrected for mean scores on all 24 items of the BPRS.
[c]Percentages displayed for each tertile represent theoretically estimated values of D_2 receptor occupancy.
*P < .06 (trend); †P < .05; ‡P < .01.
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

Figure 1. Increasing Theoretical Estimates of D_2 Receptor Occupancy, Divided in Tertiles, Are Associated With a Decrease in Mean Scores on the Positive Affect Self-Assessment Likert Scale and an Increase in Mean Scores on the Negative Affect Self-Assessment Likert Scale in Tight-Binding–Agent Users



experience in the flow of daily life of patients diagnosed with psychosis, adding ecological validity to previous studies.[8–17] However, the effect of D_2 occupancy on experience of emotions may be particularly relevant for agents that bind more tightly than dopamine to the dopamine D_2 receptor, whereas no specific associations between D_2 occupancy and emotional experience were found for looser binding agents. Given that tight- and loose-binding agents showed overlap in terms of overall receptor occupancy estimates, the results suggest that the mechanisms of D_2 receptor binding rather than mere occupancy levels of the drug play an important role in predicting experience of emotions.

Relatively Tight-Binding Versus Looser Binding Drugs and Emotional Experience

For tight-binding agents (haloperidol, risperidone), the present study found increasing levels of D_2 receptor occupancy to be associated with deteriorating emotional experience in the natural flow of daily life. These results extend previous laboratory findings that associated higher D_2 occupancy levels with worse emotional experience assessed with questionnaires in patients under antipsychotic treatment.[9,13,14]

Our findings, however, revealed no effect of D_2 occupancy levels on experience of emotions in looser binding agent (olanzapine) users, indicating that loose- and tight-binding agents have differential effects on D_2 occupancy related experience of emotions. Although several previous studies have found olanzapine to be superior to both haloperidol[22,30,31] and risperidone[22,32,33] with regard to emotional experience and quality of life, this superiority has not been confirmed in studies looking specifically at the effects of D_2 receptor occupancy on experience of emotions.[9,13,14] Results from these experimental studies, however, might be hampered by the relatively low dosage of antipsychotic medication and associated nonclinical levels of D_2 occupancy.[9] Data from our study, performed in a naturalistic sample, suggest that not the overall level of emotional experience but, rather, the distribution of emotions as a function of D_2 receptor occupancy might distinguish relatively tight-binding from looser binding agent users.

We were not able to replicate the 60%–70% D_2 occupancy window of optimal experience of reward found in haloperidol- and olanzapine-treated patients by De Haan et al.[9] However, since the vast majority of estimated patient D_2 occupancy levels were well above the upper border of this window, the current results do not rule out its existence. They only imply that it might not be detectable in a naturalistic sample of treated patients.

Differences Between Tight-Binding and Looser Binding Agents: What Is the Mechanism?

Blockade of the D_2 receptor by antipsychotics is considered to attenuate the motivational salience of not only psychotic symptoms[4] but also other experiences and thoughts and may, therefore, equally affect the dopaminergic reward system.[5] The looser binding mechanism of olanzapine, as opposed to the stringent binding mechanism of haloperidol and risperidone, allows more brief temporal binding of endogenous dopamine to the occupied D_2 receptor. Endogenous dopamine released in response to, for instance, emotional activity might, therefore, be more capable of impacting on the dopaminergic motivation and reward system in loose-binding–agent users compared to tight-binding–agent users.[22] Kapur and Seeman[34] have argued that this very mechanism of dissociation from the D_2 receptor, rather than the affinity at serotonin or other receptor sites, determines a drug's atypicality.

The observed difference in subjectively experienced side effects between olanzapine and risperidone agent users in the current study may reflect a similar mechanism. Although both atypical antipsychotics, they differ in terms of dissociation from the D_2 receptor. Similarly, this might explain the reported difference between tight- and loose-binding agents. Looser binding agents, through their mechanism of fast dissociation, may be able to maintain a certain level of well-being, even at high doses of the compound, whereas the insensitivity to endogenous dopamine associated with tighter binding agents may increasingly affect reward and emotional experience as dosage increases.

Nevertheless, blockade of 5-HT serotonin receptor sites has been suggested to be associated with a decrease in secondary negative symptoms,[35–38] and emotional experience might have been partly influenced by differences in 5-HT receptor occupancy between tight- and loose-binding–agent users. However, Kapur et al[39] showed that clinical doses of both risperidone and olanzapine resulted in 100% $5\text{-}HT_2$ receptor blockade, thus suggesting that occupancy of the serotonin receptors does not differentiate risperidone and olanzapine users. The differential effects of risperidone and olanzapine on emotional experience, as found in our naturalistic sample, are thus more likely explained by differential dissociation from the D_2 receptor rather than occupancy of the serotonin receptor. Nonetheless, it is arguable that the differential affinity for 5-HT between haloperidol and olanzapine might have influenced the observed differences in emotional experience between tighter and looser binding agent users. However, the current literature does not indicate superiority of serotonin-blocking antipsychotics over the pure dopamine antagonist haloperidol for regulating or alleviating depressive or negative symptoms.[40–42] Furthermore, Kapur and Seeman[34] have shown that, unlike D_2 receptor modulation, the mechanism of serotonin receptor antagonism is neither necessary nor sufficient in producing atypical effects, suggesting that actions at the D_2 receptor might be more closely related to emotional well-being.

Confounding of Symptom Severity or EPS

Given that patients with more severe symptomatology might receive higher doses of medication,[43] the observed decline in emotional experience in tighter binding agent users may occur as a consequence of more severe psychopathology rather than of increased D_2 receptor occupancy. For high-dose–treated patients, decreases in positive affect indeed appeared to be largely imbued with the burden of severe symptomatology. For average-dosed patients, however, the decrease in positive affect did not necessarily occur collaterally with an increase in symptoms. The experience of negative affect, on the other hand, could in no case be explained by increased symptom levels. The inability to generate positive affect, thus, seems as much a consequence of D_2 receptor occupancy as of psychopathology, whereas the induction of negative affect in high-dose–treated patients appears to originate predominantly from occupancy of the D_2 receptor. Interestingly, the ability to generate positive affect is "first" affected, at lower levels of D_2 occupancy.

Since high D_2 receptor occupancy levels are associated with increased severity of EPS,[22] feelings of negative emotional experience might be induced by the occurrence of these side effects. Extrapyramidal symptoms are considered to become evident at occupancy levels above 78%.[44] The tighter binding agent users, however, already experienced decreased feelings of positive affect at estimated D_2 occupancy levels below 78%, suggesting that differences in EPS may explain part but not all of the observed variation in subjective response. These findings are in line with results from Garcia-Cabeza et al,[22] who found that, although being a major contributor to negative subjective response, EPS could not completely explain variation in emotional experience.

Clinical Implications

Subjective response to medication has long been neglected both in clinical routine and in clinical trials of potential antipsychotic agents.[17] Symptom reduction and occurrence of extrapyramidal symptoms have long been regarded the main indicators of therapeutic outcome.[8] However, ongoing developments in medication research have led to increased attention for subjectively experienced side effects.[8] Results from our study underline the importance of the assessment of these subjective effects, since the antidopaminergic effect of antipsychotics appears to cause deterioration in well-being not necessarily related to symptom levels or EPS, particularly evident in more tight-binding–agent users. Most important, changes in emotional experience already occur in response to relatively low levels of D_2 receptor occupancy and might, therefore, act as a more sensitive and earlier indicator of adverse effects than the occurrence of EPS at 78% D_2 receptor occupancy.[44] The assessment of emotional experience gains additional relevance when considering that, next to symptom reduction and EPS, experience of emotions has been shown to be strongly associated with medication compliance and illness prognosis.[16,17,45] We, therefore, argue that assessment of emotional experience should become part of standard assessment in both clinical routine and medication trials.

It is important to note that we used only 1 compound with a loose binding profile and only 2 compounds with a tighter binding profile. Since the pattern of dissociation from the D_2 receptor is a continuous measure, the results may increase or decrease for drugs with an even looser or tighter binding potential. However, the current results suggest that the distinction between drugs that bind tighter and drugs that bind looser than dopamine to the dopamine D_2 receptor is clinically relevant, as has been found earlier in relation to parkinsonism.[20]

Strengths and Limitations

Strengths of the study are the naturalistic approach, the sample size, and the use of momentary assessment technology to investigate emotional experience in the realm of daily life. Applying the ESM has made it possible to investigate subtle, but meaningful changes in both positive and negative affect related to clinically dosed antipsychotic medication in a large sample of patients in a real world environment.

Limitations are first that no actual D_2 occupancy data were used, but, rather, occupancy was estimated based on the literature. Large metabolic interindividual variety has been found in occupancy of D_2 receptor sites[9] as well as intraindividual variety related to decay of the antipsychotic agent over time. This may induce noise in the D_2 occupancy variable. However, we expect the error term to be random, since intraindividual and interindividual variability has been found for all agents under investigation. Therefore, it may decrease the power to find a meaningful association, but it is unlikely to provide spurious associations. In addition, we have optimized the accuracy of the estimation by basing it on a large collection of published observations from the literature (see eAppendix 1). Nonetheless, the lack of direct D_2 occupancy measures calls for conservative interpretation of the data. Second, since the current study has investigated only 3 agents, of which only 1 is considered to bind loosely to the D_2 receptor, conclusions regarding the mechanism of loose and tight binding should not be generalized. Third, although EPS are assumed to become evident only at occupancy levels above 78% and therefore cannot fully explain variation in emotional experience, the lack of direct EPS assessments cannot certify that the observed associations between affect and D_2 receptor binding are truly unconfounded by variation in EPS. Fourth, subjective reports are considered less reliable, although not necessarily less valid, than objective measurements.[46] Fifth, the current study used ESM, a daily life assessment technique in which subjects have to comply with a paper-and-pencil diary protocol without the researcher being present. Recently, some authors have doubt on the reliability and subject compliance in paper-and-pencil ESM studies, favoring the use of electronic devices.[47] However, in a comparative study, Green et al[48] concluded that both methods yielded similar results. In addition, a recent study by our group using a signal-contingent random-time sampling procedure with multiple observations per day—such as the protocol used in the current study—also found evidence underscoring the validity of the paper-and-pencil random-time self-report data in the current study.[49]

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

Author affiliations: Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Center, Maastricht, The Netherlands (Prof van Os; Drs Thewissen, Bak, T. Lataster, Lardinois, Delespaul, and Myin-Germeys; and Mr J. Lataster); King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, United Kingdom (Prof van Os); Academic Medical Center, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands (Dr de Haan); Faculty of Psychology, Open University of the Netherlands, Heerlen, The Netherlands (Dr Thewissen); and School of Psychological Sciences, University of Manchester, United Kingdom (Dr Myin-Germeys).

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eAppendix 1 is available at PSYCHIATRIST.COM

eAppendix 1. Theoretical Estimation of Dopamine D_2 Receptor Occupancy

Theoretical estimates of D_2 receptor occupancy were obtained by fitting *agent-specific hyperbolic functions*, defined as D_2 receptor occupancy = Occ_{max} × [administered daily dose/(administered daily dose + ED50)],[1] to mean dose-occupancy values calculated from previous literature. *ED50* is the dose predicted to theoretically provide 50% of maximum receptor occupancy, and Occ_{max} was replaced by 100, assuming that all of the tracer used to investigate D_2 occupancy can be replaced by endogenous dopamine.[2]

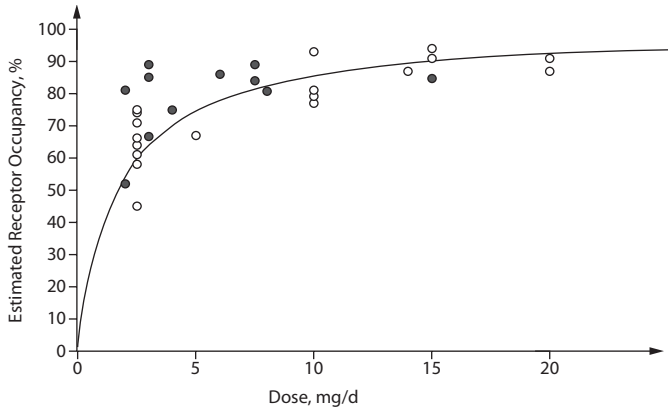
We screened the PubMed database for published studies reporting dose-D_2 occupancy data for the agents olanzapine, risperidone, and haloperidol, by using combinations of the following keywords: *olanzapine*, *risperidone*, *haloperidol*, *occupancy*, and *schizophrenia*. Only articles reporting individual dose-occupancy data points, rather than group averages, were included and further screened for additional literature. Animal studies were not included. Qualitative criteria were utilized to weight data from these studies: (1) sample size > 10, (2) investigation of D_2 receptor occupancy in striatal areas, and (3) patient sample consisting of patients diagnosed with schizophrenic disorder. Data from articles fulfilling all 3 criteria received a weight factor of 2 in the calculations, whereas articles that did not, received a weight factor of 1 (eFigures 1–3). This search strategy led to a total of 24 articles, with 10 articles (n = 99) reporting dose-occupancy measures for olanzapine users,[1–10] 9 articles (n = 84) reporting dose-occupancy measures for risperidone users,[2,10–17] and 5 articles (n = 33) reporting dose-occupancy measures for haloperidol users.[3,9,10,18,19]

Dose-occupancy measures extracted from these articles were used to calculate theoretical estimates of ED50 for haloperidol, risperidone, and olanzapine, resulting in the following hyperbolic formulas (eFigures 1–3):

- haloperidol—theoretical estimate of D_2 receptor occupancy = 100 × [daily dose/(daily dose + 1.75)]
- risperidone—theoretical estimate of D_2 receptor occupancy = 100 × [daily dose/(daily dose + 1.43)]
- olanzapine—theoretical estimate of D_2 receptor occupancy = 100 × [daily dose/(daily dose + 7.35)]

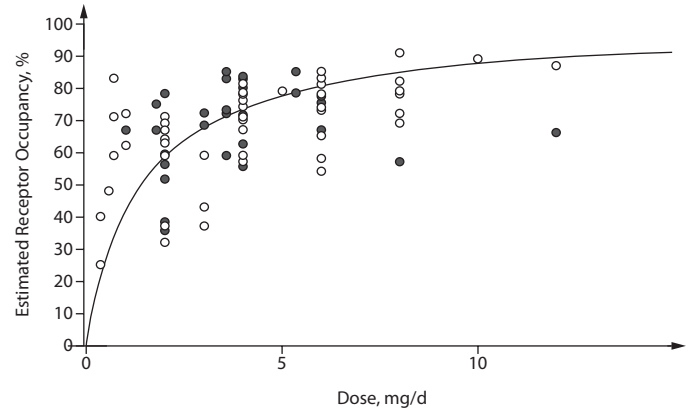
These functions were then applied to individual subject medication data extracted from the ESM medication forms (see Method) in order to predict occupancy estimates from daily medication dose for each individual subject.

eFigure 1. Theoretical Estimation of D_2 Receptor Occupancy, With Estimated Dose-Occupancy Function Displayed for the Agent Haloperidol[a]



[a]Curve fitting was based on weighted mean values of dose-occupancy data extracted from the literature (dots). White dots represent data points that received a weight factor of 2 for the calculation of mean values, whereas data represented by black dots received a weight factor of 1.

eFigure 2. Theoretical Estimation of D_2 Receptor Occupancy, With Estimated Dose-Occupancy Function Displayed for the Agent Risperidone[a]



[a]Curve fitting was based on weighted mean values of dose-occupancy data extracted from the literature (dots). White dots represent data points that received a weight factor of 2 for the calculation of mean values, whereas data represented by black dots received a weight factor of 1.

(continued)

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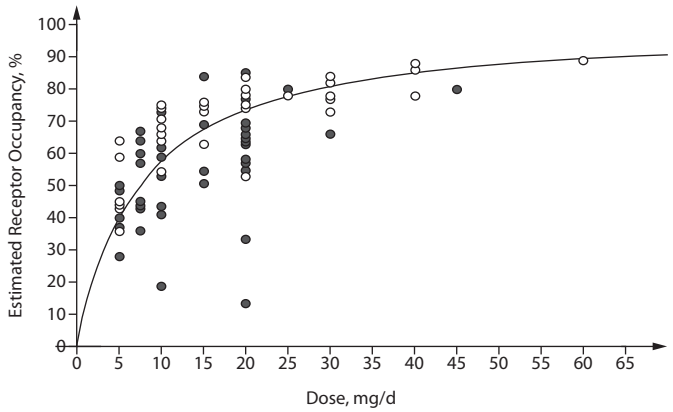
eFigure 3. Theoretical Estimation of D_2 Receptor Occupancy, With Estimated Dose-Occupancy Function Displayed for the Agent Olanzapine[a]



[a]Curve fitting was based on weighted mean values of dose-occupancy data extracted from the literature (dots). White dots represent data points that received a weight factor of 2 for the calculation of mean values, whereas data represented by black dots received a weight factor of 1.

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