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**Altered emotional experiences attributed to antipsychotic medications - A potential link with estimated dopamine D-2 receptor occupancy**

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## Altered emotional experiences attributed to antipsychotic medications – A potential link with estimated dopamine D<sub>2</sub> receptor occupancy



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## ABSTRACT

Altered emotional experiences in response to antipsychotics may increase the burden of disease in patients with schizophrenia. In a large cross-sectional study, patients with schizophrenia completed the Subjects Reaction to Antipsychotics questionnaire (SRA) to assess whether they attributed altered emotional experiences (flattened affect or depressive symptoms) to their antipsychotics. Association with antipsychotic D<sub>2</sub> receptor affinity and occupancy was examined using logistic regression. We compared antipsychotic-attributed emotional experiences between patients using antipsychotic monotherapy and combination therapy. Of the 1298 included patients, 23% attributed flattened affect to their antipsychotics and 16% attributed depressive symptoms to their antipsychotics, based on the SRA. No differences were observed between antipsychotics in patients on monotherapy. We discuss that within these patients' relatively low dose range, altered emotional experiences did not appear to relate to the level of D<sub>2</sub> receptor affinity of antipsychotic monotherapy. Patients using antipsychotic combination therapy (22%) were more likely to attribute depressive symptoms to their antipsychotics than patients using antipsychotic monotherapy (OR [95%CI] = 1.443 [1.033–2.015]); possibly due to higher D<sub>2</sub> receptor occupancies as estimated by dose equivalents.

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## 1. Introduction

Patients with schizophrenia can experience altered emotions in response to antipsychotic treatment (Fakhoury et al., 2001; Gothelf et al., 2003; Siris and Bench, 2003). Altered emotional experiences can comprise depressive symptoms, flattened emotions or inability to experience pleasure (anhedonia). These symptoms further increase the burden of disease and lead to non-adherence to antipsychotic medication (Perkins, 2002; Conley, 2009).

Antipsychotics exert at least part of their therapeutic effect by blockade of striatal dopamine receptors (Jones and Pilowsky, 2002). Animal research has shown that chronic blockade of dopamine D<sub>2</sub> receptors in mesolimbic brain areas disturb the

motivational system, which may lead to relative anhedonia (Wise, 1982; Nakajima and Patterson, 1997). A dose-dependent relationship with altered emotional experiences has been demonstrated for first generation antipsychotics in patients with schizophrenia (Krakowski et al., 1997; Perenyi et al., 1998). Several imaging studies found associations between emotional experiences and increased levels of D<sub>2</sub> receptor occupancy, determined by positron emission tomography (de Haan et al., 2000; Bressan et al., 2002; de Haan et al., 2003; Mizrahi et al., 2007). For example, exceeding a level of 70% D<sub>2</sub> receptor occupancy worsened the subjective experience (well-being) with antipsychotics (as measured by the Subjective Well-being under Neuroleptics Scale) in patients with schizophrenia treated with olanzapine or risperidone (de Haan et al., 2003). Of interest, dopamine depletion by alpha-methyl paratyrosine induced unpleasant subjective responses (dysphoric symptoms) in drug-free patients with schizophrenia as measured by the Addiction Research Center Inventory and the Drug Attitude Inventory (Voruganti et al., 2001). These result further suggested

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that individuals with a lower dopamine function at baseline are at an increased risk for dysphoric responses during antipsychotic therapy.

Lataster et al. found a significant interaction effect between high D<sub>2</sub> receptor occupancy and haloperidol, but not risperidone or olanzapine, on emotional experiences (Lataster et al., 2011). These findings imply that antipsychotics with high affinity for the D<sub>2</sub> receptor are most likely to be associated with altered emotional experiences. So far, studies reporting such associations found minimal effect sizes and included small study groups without a control group using antipsychotics with medium or weak affinity for the D<sub>2</sub> receptor (Bressan et al., 2002; Mizrahi et al., 2007; Lataster et al., 2011). It remains unknown whether antipsychotics with a weak affinity for (or rapid dissociation from) the D<sub>2</sub> receptor have a decreased risk of altering emotional experiences compared to antipsychotics with higher D<sub>2</sub> receptor affinity (Kapur and Seeman, 2000, 2001). Besides, the antagonistic effects of some antipsychotics on the serotonin 5-HT<sub>2a</sub> receptor have been proposed to mediate a reduction of depressive symptoms, possibly interacting with depressogenic effects of dopamine blockade (Möller, 2005a, 2005b).

The current study investigated the effects of six frequently prescribed antipsychotics, with distinct D<sub>2</sub> receptor affinities on emotional experiences in a large cross-sectional sample of patients with psychotic disorders. We studied the association of altered emotional experiences attributed to antipsychotics with D<sub>2</sub> receptor affinity, estimated occupancy and their interaction.

## 2. Methods

### 2.1. Subjects

We conducted a cross-sectional study in a population of adult patients with schizophrenia or related psychotic disorders, receiving mental health care in the North of the Netherlands, who participated in the annual screening program Pharmacotherapy Monitoring and Outcome Study (PHAMOUS; Schorr et al., 2009; Lako et al., 2012). The study was carried out between January 2007 and April 2010 in accordance with the Declaration of Helsinki. Altered emotional experiences in response to antipsychotics were assessed by the Subjects Reaction to Antipsychotics (SRA) self-report questionnaire, designed to measure desired and undesired effects of antipsychotics (Wolters et al., 2006). The SRA was sent out by mail prior to the PHAMOUS screening. Patients having difficulties completing the questionnaires due to concentration problems or cognitive impairment received help from the nurse during the screening.

A psychiatrist diagnosed each patient according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) classification system. The patient's psychiatrist or case manager rated the quality of mental health care service by the Health of Nations Outcome Scale (HoNOS), a 5-point Likert scale (Wing et al., 1996; Mulder et al., 2004). The HoNOS includes an item on depression, which we compared with the rating of emotional experiences. Trained nurses conducted the Positive and Negative Symptom Scale for Remission (PANSS-R) interview to assess whether the patients' psychotic symptoms were in remission, which is rated on the same 7-point Likert scale as the full version of the PANSS (Opler et al., 2007). The PANSS-R includes a "blunted affect" score (N1) which we compared with the rating of emotional experiences. Medication use over the past year was retrieved from medical records and confirmed with the patient.

We included patients with schizophrenia or a related psychotic disorder (diagnosed following DSM-IV criteria with schizophrenia, schizoaffective disorder, schizophreniform disorder, latent

schizophrenia, delusional disorder, brief psychotic disorder or not otherwise specified psychotic disorder; codes 295.4–295.9, 297.1, 298.8 and 298.9, respectively), who completed the SRA and used one of the following antipsychotics for at least one month prior to the interview: haloperidol, risperidone, olanzapine, clozapine, quetiapine or aripiprazole.

### 2.2. Rating of emotional experiences

The SRA consists of 74 items (provided by Wolters et al. (2006)) that are grouped into 9 subscales: recovery, weight gain, sexual anhedonia, sedation, affective flattening, extrapyramidal symptoms, diminished sociability and increased sleep. All items are rated on a three-point scale: no; yes-mild; yes-severe. It shows a good test-retest reliability and validity in patients with schizophrenia (Wolters et al., 2006). Factor analysis has demonstrated that emotional experiences in response to antipsychotics can be separated into the dimensions flattened affect and depressive symptoms (Lako et al., 2013a). Flattened affect was measured by the items: "my emotions are dull", "my emotions are too dull", "I am less emotional" and "my thoughts are subdued"; depressive symptoms by "I feel down" and "I feel more depressed". We evaluated the concurrent validity of the sum scores on flattened affect and depressive symptoms by comparing them with observational measures. For the flattened affect score on the SRA we calculated the correlation with the "blunted affect" score (N1) on the PANSS-R. For the depressive symptom score on the SRA we calculated the correlation with the outcome on the HoNOS depression-item. To simplify further analyses, we used dichotomized scores: flattened affect was considered present when a patient responded to all four statements about flattened affect with "yes" (mild or severe); depressive symptoms were considered present when a patient responded on both items for depression with "yes" (mild or severe).

### 2.3. Estimated antipsychotic D<sub>2</sub> receptor affinity and occupancy

#### 2.3.1. Categorisation of antipsychotic D<sub>2</sub> receptor affinity

To streamline analyses, antipsychotic mono-therapy was grouped in four levels of affinity [ $K_i$ ] for the dopamine D<sub>2</sub> receptor: high for haloperidol and risperidone ( $K_i < 1$  nM), medium for olanzapine ( $1 < K_i < 10$  nM), weak for clozapine and quetiapine ( $K_i > 10$  nM; Kapur and Seeman, 2000; Nasrallah, 2008). The fourth category consisted of aripiprazole, which has a high, but partial affinity for the D<sub>2</sub> receptor ( $K_i < 1$  nM) because of both agonistic and antagonistic effects at the D<sub>2</sub> receptor (Roth et al., 2003).

#### 2.3.2. Estimated antipsychotic D<sub>2</sub> receptor occupancy

The D<sub>2</sub> receptor occupancy was estimated by entering the daily dose of each individual subject in the antipsychotic-specific Michaelis-Menten dose-occupancy function, as described previously (Lako et al., 2013b, 2014). The doses of antipsychotic depot preparations were first converted into daily dose values. The relationship between estimated occupancy and the log odds of emotional experiences was not linear. Therefore, estimated occupancy was categorized into three levels, each containing 33% of the cases. The daily dose was additionally expressed as the defined daily dose (DDD) equivalent, according to standards of the World Health Organisation (2013) by dividing the prescribed daily dose (PDD) by the DDD (PDD/DDD). The DDD is the assumed average maintenance dose per day for a drug, used for its main indication in adults. The DDD equivalent was included to simplify comparison with other studies.

For patients using two or more antipsychotics, the level of D<sub>2</sub> receptor occupancy was estimated for each antipsychotic

separately, by applying the dose-occupancy equivalents as described above (Lako et al., 2013b) No dose-response function was available for bromperidol, fluphenazine, flupenthixol, pimozide and zuclopenthixol, the D<sub>2</sub> occupancy for these typical antipsychotics was estimated by applying dose-occupancy equivalents for haloperidol (the daily dose of zuclopenthixol was first divided by five). Occupancy could not be estimated for patients using chlorprothixene, penfluridol, perphenazine, pipamperone or sertindole. For each patient on combination therapy, we used the highest individual level of estimated occupancy in the analyses. The cumulative daily dose was expressed as the sum of the (PDD/DDD) ratios for each combination of antipsychotics (World Health Organisation, 2013).

#### 2.4. Statistics

Categorical variables were tested using a chi-square test. Continuous variables were not normally distributed and were therefore tested with the non-parametric Mann–Whitney *U* test. Correlations were calculated using Spearman's correlations. The association of altered emotional experiences with the level of antipsychotic D<sub>2</sub> receptor affinity and the estimated level of dopamine D<sub>2</sub> receptor occupancy was calculated using logistic regression analysis. Dependent variables were “flattened affect” and “depressive symptoms”. The levels of affinity and occupancy, and the individual six antipsychotics were entered as categorical variables. Affinity and occupancy were first entered separately in two models for patients on antipsychotic monotherapy. Then we built a regression model with both entered simultaneously, to study their independent associations with altered emotional experiences, i.e. adjusted for each other. Next, we studied a potential interaction effect between affinity and occupancy by adding their product term as an independent variable to the final model. The effects of individual antipsychotics were compared in an additional model by entering the six antipsychotics as a categorical independent variable with haloperidol as the reference category.

We compared the effect of antipsychotic monotherapy with combination therapy on both flattened affect and depressive symptoms in a separate analysis. The goodness of fit of each model was evaluated using the Hosmer–Lemeshow test. Statistical analyses were performed using Statistical Package for Social Sciences (PASW-18). A two-tailed *p*-value of *p* < 0.05 was accepted as statistically significant.

### 3. Results

#### 3.1. Subjects

Out of 2241 patients with psychotic disorders, 142 (6%) were antipsychotic-free, 200 (9%) did not use one of the selected antipsychotics, 36 (2%) had incomplete information on antipsychotic dose and 565 (25%) did not complete (the selected items of) the SRA questionnaire. In total, *n* = 1298 patients were included in the study (Table 1).

#### 3.2. Altered emotional experiences

Of the 1298 included patients, 199 (15%) subjectively attributed flattened affect to antipsychotic treatment; 109 (8%) depressive symptoms, and 103 (8%) attributed both to antipsychotics. Male patients attributed flattened affect, but not depressive symptoms, more frequently to antipsychotics than female patients ( $\chi^2(1) = 4.80$ ; OR [95%CI] = 1.38 [1.03–1.85], *p* < 0.05). Patients who received antidepressants had a higher probability of attributing depressive symptoms ( $\chi^2(1) = 6.60$ ; OR [95%CI] = 1.51 [1.10–2.07],

**Table 1**  
Patient characteristics (*N* = 1298).

	N or mean	% or SD
Gender, male	901	69%
Gender, female	397	31%
Years of age (mean;SD)	40.0	11.0
Years of illness (mean; SD)	13.4	9.9
Treatment Status		
Outpatients	791	62%
Inpatients (acute and chronic)	245	19%
Sheltered Housing Facilities	251	20%
Diagnosis		
Schizophrenia diagnosis	919	70%
Schizoaffective disorder	155	12%
Other psychotic disorder	224	7%
Psychotic symptoms (PANSS-R)		
Positive (mean; SD)	2.3	1.1
Negative (mean; SD)	2.1	1.0
Antipsychotic medication		
Monotherapy	1010	78%
Combination therapy	288	22%
Co-medication (number; SD)	2.0	2.2
Antidepressants	348	27%
Benzodiazepines	303	23%
Anticholinergics	168	13%
Mood stabilizers	71	6%
Sleep medication	134	10%

*p* < 0.01), but not flattened affect, to antipsychotics. Perceived flattened affect attributed to antipsychotic treatment correlated weakly with flattened affect on the PANSS-N1 (*n* = 1260 (97%), *r* [95%CI] = 0.11 [0.05–0.16], *p* < 0.01); perceived depressive symptoms attributed to antipsychotics correlated weakly with depressive symptoms on the HoNOS (*n* = 1072 (83%), *r* [95%CI] = 0.22 [0.16–0.28], *p* < 0.01).

#### 3.3. Antipsychotic monotherapy

Antipsychotic monotherapy was used by *n* = 1010 (78%) patients (Table 1). Depot formulations were used by 34 (40%) of the haloperidol users and by 92 (31%) of the risperidone users. The level of estimated D<sub>2</sub> receptor occupancy among patients with antipsychotic mono-therapy was categorized in the following three intervals: [0.1–48.3%]; [48.3–71.1%]; [71.1–89.0%]. Logistic regression showed no relationship between the antipsychotic D<sub>2</sub> receptor affinity and altered emotional experiences in patients using antipsychotic mono-therapy. There was neither a relationship when corrected for binding affinity, nor an interaction effect between binding affinity and estimated D<sub>2</sub> receptor occupancy and altered emotional experiences attributed to antipsychotics.

The six individual antipsychotics were compared, no statistically significant differences were observed.

#### 3.4. Antipsychotic combination therapy

Antipsychotic combination therapy was prescribed to 288 (22%) of the patients, of which 20 patients used a combination of three antipsychotics. Most frequently prescribed were combinations with clozapine (42 patients; 49%) or depot preparations (67 patients; 23%). The maximal level of estimated D<sub>2</sub> receptor occupancy was determined for 275 (95%) of the patients using combination therapy. The remainder used medication for which no dose-occupancy equivalents were available. The mean estimated D<sub>2</sub> receptor occupancy for patients on combinations (74%; SD11.5) was higher than for patients on mono-therapy (58.0%; SD19.8; *p* < 0.001), see Table 2. In addition, patients using combination therapy had higher mean PDD/DDD ratios than patients using antipsychotic monotherapy (*p* < 0.001). Patients using

**Table 2**  
Antipsychotic treatment was categorized into four levels of D<sub>2</sub> receptor affinity or combination therapy (N=1298). The number of patients attributing flattened affect or depressive symptoms to antipsychotics was given for each treatment group. PDD/DDD=mean prescribed daily dose divided by defined daily dose; D<sub>2</sub>R Occ.=mean estimated level of D<sub>2</sub> receptor occupancy; for patients using antipsychotic combination therapy only the mean maximal level of each combination was displayed as indicated by an asterisk (\*); Antidepr.=antidepressant use; D<sub>2</sub>R Affinity=D<sub>2</sub> receptor affinity class.

Antipsychotic (N)	Dose, mg [mean;SD]	PDD/DDD [mean]	D <sub>2</sub> R Occ. [mean %]	Antidepr. [N;%]	Flattened [N;%]	Depressive [N;%]	D <sub>2</sub> R Affinity (N)	Flattened [N;%]	Depressive [N;%]
Haloperidol (57)	4.07 (± 4.24)	0.9	74	15 (26)	16 (28)	10 (18)	High (355)	87 (25)	54 (15)
Risperidone (298)	3.69 (± 3.72)	0.8	66	58 (19)	71 (24)	44 (15)	Medium (276)	55 (20)	43 (16)
Olanzapine (276)	13.7 (± 7.3)	1.4	61	77 (28)	55 (20)	43 (16)			
Clozapine (197)	317 (± 163)	1.1	42	60 (30)	45 (23)	38 (19)	Weak (301)	66 (22)	46 (15)
Quetiapine (104)	486 (± 315)	1.2	26	34 (33)	21 (20)	8 (8)	Partial (78)	17 (22)	10 (13)
Aripiprazole (78)	16.8 (± 7.0)	1.1	85	15 (19)	17 (22)	10 (13)			
Mean monotherapy (1010)		1.1	58	259 (26)	225 (22)	153 (15)			
Combination therapy (288)		~2.3	74*	89 (31)	77 (27)	59 (21)			

antipsychotic combination therapy were more likely to attribute depressive symptoms to their antipsychotic medication ( $\chi^2(1)=4.47$ , OR [95%CI]=1.443 [1.033–2.015]), but not flattened affect. This effect remained significant when adjusted for gender and antidepressant use ( $\chi^2(3)=10.98$ , OR [95%CI]=1.420 [1.015–1.986]).

#### 4. Discussion

We investigated antipsychotic-attributed emotional experiences and their relationship with antipsychotic D<sub>2</sub> receptor affinity and estimated occupancy in a large sample of patients with psychotic disorders. Overall, 31% attributed altered emotional experiences to their antipsychotic treatment. The antipsychotics in the sample, including quetiapine, clozapine and aripiprazole, represented a wide range of D<sub>2</sub> receptor affinities. At the investigated dose ranges, the attribution of altered emotional experiences appeared to be comparable between antipsychotic monotherapy treatments. Also the antipsychotic D<sub>2</sub> receptor affinity appeared to be unrelated to altered emotional experiences. Given that the investigated dose ranges were relatively low, potential differences between low-dose antipsychotic monotherapy treatments in altering emotional experiences may thus be marginal in clinical practice.

Previous associations between antipsychotics and altered emotional experiences have predominantly been demonstrated in patients receiving relatively high doses of antipsychotics with a high affinity for the D<sub>2</sub> receptor, resulting in high levels of occupancy (Van Putten and May, 1978; Perenyi et al., 1998; Bressan et al., 2002). While some *in vivo* studies have described an association between subjective wellbeing and D<sub>2</sub> receptor binding in patients on low-dose antipsychotics (de Haan et al., 2000, 2003), in another study (Mizrahi et al., 2007) associations were limited to patients using higher dosages of these antipsychotics than observed in our study. Takeuchi et al. (2013) compared estimated D<sub>2</sub> occupancy with subjective experience/drug attitude in 371 patients after 6 months on risperidone, olanzapine or ziprasidone. Occupancy was estimated from plasma concentrations. Comparable to our findings, in the pooled sample, no association was found between D<sub>2</sub> occupancy and subjective experience/drug attitude as measured with the Drug Attitude inventory (DAI-10).

In our sample, patients using antipsychotics with high affinity for the D<sub>2</sub> receptor received recommended doses of about 4 mg haloperidol or risperidone, corresponding with intermediate levels of estimated D<sub>2</sub> receptor occupancy (below 90%, APA Guidelines, 2006; Trimbo-Institute, 2010). Possible ceiling effects could therefore not be detected. Perhaps current prescription behavior of antipsychotics with high D<sub>2</sub> receptor affinity has been adjusted to

the side effect profile.

The increased likelihood of patients using antipsychotic combination therapy attributing depressive symptoms to antipsychotics compared to patients using monotherapy could suggest involvement of D<sub>2</sub> receptor occupancy at higher doses. In accordance with previous studies (Procyshyn et al., 2001; Barbui et al., 2007), the cumulative daily dose of most patients using antipsychotic combination therapy exceeded a rate of 1.5 times the Defined Daily Dose of the World Health Organisation (2013). Consequently, the estimated level of D<sub>2</sub> receptor occupancy in patients receiving combination therapy was high, which may support a relationship between high levels of D<sub>2</sub> receptor occupancy and altered emotional experiences (de Haan et al., 2000, 2003; Bressan et al., 2002; Mizrahi et al., 2007). More detailed analysis of estimated D<sub>2</sub> receptor occupancy in relation with attributed emotional experiences in patients receiving combination therapy could not be performed, because the combinations were diverse and different interactions between antipsychotics may have distinct effects on receptor occupancy. The current result that patients using antipsychotic combination therapy attribute depressive symptoms to their antipsychotics demands more study of the risks and benefits of combination therapy.

Besides our dopaminergic D<sub>2</sub> hypothesis, the affinity of second generation antipsychotics for the serotonin 5-HT<sub>2A</sub> receptor could influence altered emotional responses (Siris, 2000; Naber et al., 2001; Möller, 2005a, 2005b; Leucht et al., 2009). First generation antipsychotics lacking affinity for this receptor would be more likely to have depressogenic effects (Möller, 2005a, 2005b). However, the serotonin hypothesis is under debate, since multiple studies failed to detect a differential effect between antipsychotics in the treatment of depressive symptomatology (Furtado and Srihari, 2008; Addington et al., 2011; Rybakowski et al., 2012). Likewise, our study did not find differences between users of first and second generation antipsychotics on emotional experiences attributed to antipsychotics. Thus potential modulating effects are unlikely to be dependent on serotonin transmission alone (Meltzer and Huang, 2008). In addition to serotonergic activities, antipsychotics also show varying degrees of anticholinergic, antihistaminergic and GABAergic activities (e.g. Stahl, 2013), which could have an impact on emotional experiences attributed to antipsychotic medications. As we did not expect major effects from these activities they were not considered in our analysis; the more as we did not observe any differences between the individual antipsychotics.

Altered emotional experiences in response to antipsychotics were investigated from the patient's perspective. Consistent with our work, a preceding study shows that patients on clozapine combination therapy were more likely to experience affective flattening than patients on clozapine monotherapy as measured by

the Liverpool University Neuroleptic Side Effect Rating Scale (LUNTERS) self-report scale (Seppälä et al., 2015). The agreement of the SRA with observational measures of emotional experiences was low in the current study, which may underline the differences between self-report and interview assessment (Lindenmayer et al., 1992; Naber et al., 2001). This could also reflect patients experiencing these emotional states not always attributing them to their antipsychotics. The distinction between observational and subjective experiences is particularly relevant in patients with schizophrenia, as the prevalence of depression is high in this population (e.g. Boter et al., 2010). Future work should elucidate to what extent patients have negative emotional experiences that they do not attribute to their antipsychotics. Self-report can be preferred for the rating of emotional experiences, since some parts of the patients' affective state are difficult to measure by observational ratings, and the patients' attribution of treatment effects has found to be predictive for satisfaction and adherence to their treatment (Naber et al., 1994; Awad et al., 1996).

A potential limitation of our study was that we estimated D<sub>2</sub> receptor based on dose equivalents, instead of measuring occupancy *in vivo*. Future *in vivo* studies should confirm the current results. However, we analyzed data of  $n = 1010$  patients, a sample size which will be challenging to reach for *in vivo* measurements.

Another potential limitation of our study is that we did not control for the level of extrapyramidal symptoms experienced during treatment; symptom severity; the lifetime duration of antipsychotic treatment; or treatment compliance. As these data were not easily available we could not compare them between the treatment groups. We also did not control for the level of negative symptoms experienced before starting treatment. Doctors may prescribe certain antipsychotics less often to patients experiencing depressive symptoms prior to treatment start, because flattened affect is a known side-effect. All these factors could affect the emotional experiences and may have confounded our results. However, as no clear differences between treatment groups were observed for any of the analyzed variables including demographics, duration of illness and antidepressant use, we do not expect any of these to have a major effect. Future studies should confirm that these factors do not obscure any association with the level of D<sub>2</sub> receptor affinity or occupancy.

To conclude, our study showed that a considerable number of patients with schizophrenia (31% of our sample) attributed negative emotional experiences to their antipsychotic medication. We did not find an association between these experiences and the level of D<sub>2</sub> receptor affinity or estimated occupancy in patients with antipsychotic monotherapy, but patients used relatively low doses of antipsychotics resulting in low estimated occupancy. The increased likelihood of patients using antipsychotic combination therapy attributing depressive symptoms to their antipsychotics suggests that an association between attributed emotional experiences and the level of D<sub>2</sub> receptor affinity or occupancy could be present at high D<sub>2</sub> receptor occupancies. We recommend being cautious with prescribing combination therapy, especially when leading to high D<sub>2</sub> occupancies, to avoid depressive symptoms in response to treatment with antipsychotics.

## Contributors

IML, KT, ERvdH, HB, DW, CJS, HK & RB contributed to the design of the study. IML analyzed the data. All authors contributed to interpretation of the data and writing the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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## References

- Addington, D.E., Mohamed, S., Rosenheck, R.A., Davis, S.M., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Lieberman, J.A., 2011. Impact of second-generation antipsychotics and perphenazine on depressive symptoms in a randomized trial of treatment for chronic schizophrenia. *J. Clin. Psychiatry* 72, 75–80.
- APA Guidelines, 2006. Practice Guidelines for the Treatment of Psychiatric Disorders, Compendium. American Psychiatric Association, Arlington 2nd edition.
- Awad, A.G., Voruganti, L.N., Heslegrave, R.J., Hogan, T.P., 1996. Assessment of the patient's subjective experience in acute neuroleptic treatment: implications for compliance and outcome. *Int. Clin. Psychopharmacol.* 11, s55–s59.
- Barbui, C., Biancosino, B., Esposito, E., Marmai, L., Donà, S., Grassi, L., 2007. Factors associated with antipsychotic dosing in psychiatric inpatients: a prospective study. *Int. Clin. Psychopharmacol.* 22, 221–225.
- Boter, H., Derks, E.M., Fleischacker, W.W., Davidson, M., Kahn, R.S., EUFEST Study Group, 2010. Generalizability of the results of efficacy trials in first-episode schizophrenia: comparisons between subgroups of participants of the European First Episode Schizophrenia Trial (EUFEST). *J. Clin. Psychiatry* 71, 58–65.
- Bressan, R.A., Costa, D.C., Jones, H.M., Ell, P.J., Pilowsky, L.S., 2002. Typical antipsychotic drugs-D(2) receptor occupancy and depressive symptoms in schizophrenia. *Schizophr. Res.* 56, 31–36.
- Conley, R.R., 2009. The burden of depressive symptoms in people with schizophrenia. *Psychiatr. Clin. North Am.* 32, 853–861.
- Fakhoury, W.K., Wright, D., Wallace, M., 2001. Prevalence and extent of distress of adverse effects of antipsychotics among callers to a United Kingdom National Mental Health Helpline. *Int. Clin. Psychopharmacol.* 16, 153–162.
- Furtado, V.A., Srihari, V., 2008. Atypical antipsychotics for people with both schizophrenia and depression. *Cochrane Database Syst. Rev.*, CD005377
- Gothelf, D., Apter, A., Reidman, J., Brand-Gothelf, A., Bloch, Y., Gal, G., Kikinzon, L., Tyano, S., Weizman, R., Ratzoni, G., 2003. Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. *J. Neural Transm.* 110, 545–560.
- de Haan, L., Lavalaye, J., Linszen, D., Dingemans, P.M., Booij, J., 2000. Subjective experience and striatal dopamine D(2) receptor occupancy in patients with schizophrenia stabilized by olanzapine or risperidone. *Am. J. Psychiatry* 157, 1019–1020.
- de Haan, L., van Bruggen, M., Lavalaye, J., Booij, J., Dingemans, P.M., Linszen, D., 2003. Subjective experience and D<sub>2</sub> receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. *Am. J. Psychiatry* 160, 303–309.
- Jones, H.M., Pilowsky, L.S., 2002. Dopamine and antipsychotic drug action revisited. *Br. J. Psychiatry*, 271–275.
- Kapur, S., Seeman, P., 2000. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. *J. Psychiatry Neurosci.* 25, 161–166.
- Kapur, S., Seeman, P., 2001. Does fast dissociation from the dopamine D(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. *Am. J. Psychiatry* 158, 360–369.
- Krakowski, M., Czobor, P., Volavka, J., 1997. Effect of neuroleptic treatment on depressive symptoms in acute schizophrenic episodes. *Psychiatry Res.* 71, 19–26.
- Lako, I.M., van den Heuvel, E.R., Knegetering, H., Bruggeman, R., Taxis, K., 2013b. Estimating dopamine D2 receptor occupancy for doses of eight antipsychotics. A meta-analysis. *J. Clin. Psychopharmacol.* 33, 675–681.
- Lako, I.M., Liemburg, E.J., Van den Heuvel, E.R., Knegetering, H., Bruggeman, R., Taxis, K., 2014. Estimating dopamine D(2) receptor occupancy for doses of 8 antipsychotics: a meta-analysis: a reply. *J. Clin. Psychopharmacol.* 34, 532–533.
- Lako, I.M., Taxis, K., Bruggeman, R., Knegetering, H., Burger, H., Wiersma, D., Slooff, C. J., 2012. The course of depressive symptoms and prescribing patterns of antidepressants in schizophrenia in a one-year follow-up study. *Eur. Psychiatry* 27, 240–244.
- Lako, I.M., Bruggeman, R., Liemburg, E.J., van den Heuvel, E.R., Knegetering, H., Slooff, C.J., Wiersma, D., Taxis, K., 2013a. A brief version of the Subjects' Response to Antipsychotics questionnaire to evaluate treatment effects. *Schizophr. Res.* 147, 175–180.
- Lataster, J., van Os, J., de Haan, L., Thewissen, V., Bak, M., Lataster, T., Lardinois, M., Delespaul, P.A., Myin-Germeyns, I., 2011. Emotional experience and estimates of D(2) receptor occupancy in psychotic patients treated with haloperidol, risperidone, or olanzapine: an experience sampling study. *J. Clin. Psychiatry* 72, 1397–1404.
- Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C., Davis, J.M., 2009. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 373, 31–41.
- Lindenmayer, J.P., Kay, S.R., Plutchik, R., 1992. Multivantaged assessment of depression in schizophrenia. *Psychiatry Res.* 42, 199–207.

- Möller, H.J., 2005a. Antidepressive effects of traditional and second generation antipsychotics: a review of the clinical data. *Eur. Arch. Psychiatry Clin. Neurosci.* 255, 83–93.
- Möller, H.J., 2005b. Antipsychotic and antidepressive effects of second generation antipsychotics: two different pharmacological mechanisms? *Eur. Arch. Psychiatry Clin. Neurosci.* 255, 190–201.
- Meltzer, H.Y., Huang, M., 2008. In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. *Prog. Brain Res.* 172, 177–197.
- Mizrahi, R., Rusjan, P., Agid, O., Graff, A., Mamo, D.C., Zipursky, R.B., Kapur, S., 2007. Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia. *Am. J. Psychiatry* 164, 630–637.
- Mulder, C.L., Staring, A.B.P., Loos, J., Buwalda, V.J.A., Kuijpers, D., Sytma, S., Wierdsma, A.I., 2004. De Health of the Nation Outcome Scales (HoNOS) als instrument voor 'routine outcome assessment'. *Tijdschr. voor Psychiatr.* 24, 273–284.
- Naber, D., Walther, A., Kircher, T., Hayek, D., Holzbach, R., 1994. Subjective effects of neuroleptics predict compliance. In: Gaebel, W., Ward, A.G. (Eds.), *Prediction of Neuroleptic Treatment Outcome in Schizophrenia: Concepts and Methods*. Springer-Verlag, Vienna, pp. 85–98.
- Naber, D., Moritz, S., Lambert, M., Pajonk, F.G., Holzbach, R., Mass, R., Andresen, B., 2001. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. *Schizophr. Res.* 50, 79–88.
- Nakajima, S., Patterson, R.L., 1997. The involvement of dopamine D2 receptors, but not D3 or D4 receptors, in the rewarding effect of brain stimulation in the rat. *Brain Res.* 760, 74–79.
- Nasrallah, H.A., 2008. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol. Psychiatry* 13, 27–35.
- Opler, M.G., Yang, L.H., Caleo, S., Alberti, P., 2007. Statistical validation of the criteria for symptom remission in schizophrenia: preliminary findings. *BMC Psychiatry* 7, 35.
- Perenyi, A., Norman, T., Hopwood, M., Burrows, G., 1998. Negative symptoms, depression, and parkinsonian symptoms in chronic, hospitalised schizophrenic patients. *J. Affect. Disord.* 48, 163–169.
- Perkins, D.O., 2002. Predictors of noncompliance in patients with schizophrenia. *J. Clin. Psychiatry*, 1121–1128.
- Procyshyn, R.M., Kennedy, N.B., Tse, G., Thompson, B., 2001. Antipsychotic polypharmacy: a survey of discharge prescriptions from a tertiary care psychiatric institution. *Can. J. Psychiatry* 46, 334–339.
- Roth, B.L., Sheffler, D., Potkin, S.G., 2003. Atypical antipsychotic drug actions: unitary or multiple mechanisms for 'atypicality'? *Clin. Neurosci. Res.* 3, 108–117.
- Rybakowski, J.K., Vansteelandt, K., Szafranski, T., Thys, E., Jarema, M., Wolfgang Fleischhacker, W., Kahn, R.S., Peuskens, J., EUFEST Study Group, 2012. Treatment of depression in first episode of schizophrenia: results from EUFEST. *Eur. Neuropsychopharmacol.* 24, 1500–1505.
- Schorr, S.G., Slooff, C.J., Bruggeman, R., Taxis, K., 2009. The incidence of metabolic syndrome and its reversal in a cohort of schizophrenic patients followed for one year. *J. Psychiatr. Res.* 43, 1106–1111.
- Seppälä, N., Leinonen, E., Viikki, M., Solismaa, A., Nuolivirta, T., Kampman, O., 2015. Factors associated with subjective side-effects during clozapine treatment. *Nord. J. Psychiatry* 69, 161–166.
- Siris, S.G., 2000. Depression in schizophrenia: perspective in the era of "Atypical" antipsychotic agents. *Am. J. Psychiatry* 157, 1379–1389.
- Siris, S.G., Bench, C., 2003. Depression and schizophrenia. In: Hirsch, S.R., Weinberger, D. (Eds.), *Schizophrenia*, 2nd ed. Blackwell, Oxford, pp. 140–167.
- Stahl, S.M., 2013. *Stahl's Essential Psychopharmacology-Neuroscientific Basis and Practical Applications*, 4th revised Cambridge University Press, United States.
- Takeuchi, H., Suzuki, T., Bies, R.R., Remington, G., Mamo, D.C., Pollock, B.G., Mimura, M., Uchida, H., 2013. Estimated dopamine D2 receptor occupancy from plasma concentrations of atypical antipsychotics and subjective experience/drug attitude in schizophrenia: an analysis of the CATIE data. *Schizophr. Res.* 150, 373–379.
- Trimbos-Institute, 2010. *Multidisciplinary Guideline for Schizophrenia*. Trimbos-Institute, Utrecht.
- Van Putten, T., May, R.P., 1978. "Akinetic depression" in schizophrenia. *Arch. Gen. Psychiatry* 35, 1101–1107.
- Voruganti, L., Slomka, P., Zabel, P., Costa, G., So, A., Mattar, A., Awad, A.G., 2001. Subjective effects of AMPT-induced dopamine depletion in schizophrenia: correlation between dysphoric responses and striatal D(2) binding ratios on SPECT imaging. *Neuropsychopharmacology* 25, 642–650.
- Wing, J.K., Curtis, R.H., Beevor, A.S., 1996. *HoNOS: Health of Nations Outcome Scales. Trainers' Guide*. Royal College of Psychiatrists, London.
- Wise, R.A., 1982. Neuroleptics and operant behavior: the anhedonia hypothesis. *Behav. Brain Sci.* 5, 39–87.
- Wolters, H.A., Knegtering, R., Wiersma, D., van den Bosch, R.J., 2006. Evaluation of the subjects' response to antipsychotics questionnaire. *Int. Clin. Psychopharmacol.* 21, 63–69.
- World Health Organisation (WHO), 2013. *ATC/DDD Index 2011*. Available at: ([http://www.whocc.no/atc\\_ddd\\_index/](http://www.whocc.no/atc_ddd_index/)), last accessed: 30.09.15.