Threshold of Dopamine $D_{2/3}$ Receptor Occupancy for Hyperprolactinemia in Older Patients With Schizophrenia

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ABSTRACT

Objective: Although hyperprolactinemia carries a long-term risk of morbidity, the threshold of dopamine $D_{2/3}$ receptor ($D_{2/3}R$) occupancy for hyperprolactinemia has not been investigated in older patients with schizophrenia. Data were taken from a positron emission tomography (PET) study conducted between August 2007 and August 2015. The present post hoc study included 42 clinically stable outpatients with schizophrenia (*DSM-IV*) (mean ± SD age = 60.2 ± 6.7 years) taking olanzapine or risperidone. Subjects underwent [^{11}C]-raclopride PET scans to measure $D_{2/3}R$ occupancy before and after reducing their dose of antipsychotic by up to 40%. Blood samples were collected before each PET scan to measure prolactin levels.

Methods: The relationship between prolactin levels and $D_{2/3}R$ occupancy was examined using stepwise linear regression analyses. The $D_{2/3}R$ occupancy thresholds for hyperprolactinemia were explored using Fisher exact tests.

Results: Prolactin levels decreased following dose reduction (mean ± SD = 24.1 ± 30.2 ng/mL to 17.2 ± 15.1 ng/mL; $P < .001$). Prolactin levels were associated with female gender ($\beta = .32$, $P = .006$, vs male), antipsychotics ($\beta = .23$, $P = .02$, risperidone vs olanzapine), and $D_{2/3}R$ occupancy ($\beta = .23$, $P = .04$). Those with $D_{2/3}R$ occupancy of 66% or higher were more likely to have hyperprolactinemia than those with $D_{2/3}R$ occupancy lower than 66% ($P = .03$). Sensitivity, specificity, positive predictive value, and negative predictive value of this threshold were 0.44, 0.81, 0.78, and 0.48, respectively. We identified a $D_{2/3}R$ occupancy threshold for hyperprolactinemia of 66% in older patients with schizophrenia, which is lower than that reported in younger patients (73%) by other researchers.

Conclusions: Our results suggest a higher sensitivity to antipsychotics in older patients. Prolactin levels could assist in the determination of appropriate antipsychotic dosing to minimize adverse effects.

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Schizophrenia is a lifelong illness that typically requires maintenance antipsychotic treatment over the life span.[1] One common side effect induced by most antipsychotics is hyperprolactinemia.[2] Hyperprolactinemia can result in gonadal dysfunctions such as amenorrhea, galactorrhea, infertility, erectile dysfunction, ejaculation deficiency, and loss of libido.[3,4] Hyperprolactinemia can also lead to metabolic problems such as insulin resistance,[5] weight gain, and obesity,[6–8] which in turn may contribute to cardiovascular morbidity and mortality in this frail population.[9] Moreover, some previous studies have suggested that long-term hyperprolactinemia may be associated with decreased bone mineral density[10,11] and an increased risk of breast cancer[12] in postmenopausal women. Decreased bone mineral density, in particular, becomes more problematic in later life due to the heightened risk of falls in the elderly.[13,14] Importantly, these adverse effects may contribute to medication nonadherence during maintenance treatment.[15]

Antipsychotics can induce hyperprolactinemia by blocking dopamine $D_{2/3}$ receptors ($D_{2/3}R$) on the lactotroph cells in the anterior pituitary gland, which lies outside the blood-brain barrier.[16,17] Arakawa et al[18] demonstrated that $D_{2/3}R$ occupancy measured by positron emission tomography (PET) in the pituitary gland was associated with serum prolactin levels in 11 healthy males and 24 males with schizophrenia ($r = 0.62$, $P = .001$). Tsuboi et al[19] explored the relationship between striatal $D_{2/3}R$ occupancy and hyperprolactinemia in 481 patients with chronic schizophrenia treated with atypical antipsychotics by applying population pharmacokinetic models to a dataset from the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) study. This group[19] found that an estimated D_2R occupancy threshold of 73% was the most accurate for hyperprolactinemia in patients with chronic schizophrenia.

Although there appears to be a well-established association between $D_{2/3}R$ occupancy and hyperprolactinemia, the effects of age on this relationship are unclear. Several in vivo brain imaging studies suggest that striatal $D_{2/3}R$ availability in patients with schizophrenia decreases with age at a rate similar to that observed in healthy controls.[20–22] This may, in turn,

Clinical Points

- Hypersensitivity to antipsychotics is suggested in older patients with schizophrenia.
- Whether the dopamine $D_{2/3}$ receptor occupancy threshold for hyperprolactinemia is lower in older patients than in younger patients has been unclear.
- The $D_{2/3}$ receptor occupancy levels shown by this imaging study in older patients with schizophrenia are comparatively lower than levels previously reported in younger patients.
- Clinicians should regularly monitor prolactin levels to minimize exposure to antipsychotics.

contribute to age-related hypersensitivity to antipsychotic-induced adverse effects, including parkinsonism, tardive dyskinesia, and falls.[13,14] These findings support the clinically recommended use of lower doses of antipsychotics in older patients with schizophrenia.[23] Similarly, we recently reported that the $D_{2/3}R$ occupancy threshold for extrapyramidal symptoms in this specific population was 70%, which is 10% lower than that in younger patients.[24]

To date, no study has investigated the $D_{2/3}R$ occupancy threshold for hyperprolactinemia in older patients with schizophrenia. On the basis of the reduced $D_{2/3}R$ availability in later life and the association between extrapyramidal symptoms and lower $D_{2/3}R$ occupancy in older patients, we hypothesized that hyperprolactinemia would similarly be associated with a lower $D_{2/3}R$ occupancy threshold in later life than that established in younger adults with schizophrenia. To test this hypothesis, we conducted an analysis using the data from our previously published PET study[24–26] to examine the relationship between $D_{2/3}R$ occupancy and hyperprolactinemia in older patients with schizophrenia who were receiving either olanzapine or risperidone.

METHODS

Subjects and Settings

As reported elsewhere, a PET study[24–26] was conducted at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario, Canada, between August 2007 and August 2015. Subjects were recruited following referral by the treating physician or self-referral in response to approved advertisements, considering characteristics of potential subjects such as (1) age ≥ 50 years, (2) no hospitalization within 6 months, and (3) single antipsychotic intake (olanzapine ≥ 10 mg/day or risperidone ≥ 2 mg/day). This study was approved by the CAMH Research Ethics Board and Health Canada, and all subjects provided written informed consent after complete description of the study. This study was registered at ClinicalTrials.gov (identifier: NCT00716755).

The present study was a post hoc analysis of a 12- to 24-week prospective PET study,[24–26] which was conducted to examine the effects of antipsychotic dose reduction in older, stable patients with schizophrenia (Supplementary eFigure 1). Details of the study procedure, including selection criteria, are described elsewhere.[24–26] Briefly, subjects were clinically stable outpatients aged 50 years and older who met *DSM-IV*[27] (Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition[28]) criteria for either schizophrenia or schizoaffective disorder and who had been continuously treated with olanzapine (≥ 10 mg/day) or risperidone (≥ 2 mg/day). Patients were excluded if they were incapable of providing informed consent, had a history of treatment with a depot antipsychotic, met criteria for substance abuse within 6 months of the study, had a positive urine drug screen, or had a significant neurologic or general medical condition.

Study Description

Following initial clinical assessments, venous blood was collected before the baseline [^{11}C]-raclopride PET scan. Then, the daily dose of olanzapine and risperidone was reduced to a target dose that was up to 40% lower than the baseline daily dose, but still higher than the lowest doses endorsed in an expert consensus guideline[23] for older patients with schizophrenia: 7.5 mg/day for olanzapine and 1.5 mg/day for risperidone. All other psychotropics were kept constant throughout the study. At least 2 weeks after the dose reduction was completed, subjects underwent a [^{11}C]-raclopride PET scan, and another blood sample was taken. Blood samplings were not performed at the same time of the day before and after the dose reduction.

Prolactin levels were assayed using a chemiluminescent immunoassay (Access Immunoassay System, Prolactin 33530). Hyperprolactinemia was defined as > 18.77 ng/mL for men and > 24.20 ng/mL for women.[29] We calculated prolactin unit levels by dividing prolactin levels by the threshold of hyperprolactinemia for each gender. Neither postmenopausal status nor menstrual cycle was utilized to evaluate hyperprolactinemia.

Psychopathology and adverse effects were assessed at the baseline PET visit and the postreduction PET visit. The assessments for psychopathology included the Brief Psychiatric Rating Scale (BPRS)[30] and Positive and Negative Syndrome Scale (PANSS).[31] The assessments for adverse effects included the Abnormal Involuntary Movement Scale (AIMS),[32] Simpson-Angus Scale (SAS),[33] Subjective Well-Being Under Neuroleptic Treatment Scale (SWN),[34] and Barnes Akathisia Scale (BAS).[35]

PET Image Acquisition and Analysis

Subjects underwent [^{11}C]-raclopride PET scans approximately 15 hours after the last dose of olanzapine or risperidone. The postreduction PET scans were completed at least 2 weeks after the antipsychotic target dose was reached. PET and magnetic resonance imaging and data analysis procedures were recently published.[24] $D_{2/3}R$ occupancy was estimated using the measure of binding potential relative to the nondisplaceable compartment (BP_{ND}), which was estimated using the cerebellum as the reference region. The reliability of BP_{ND} quantification of $D_{2/3}R$ occupancy in the longitudinal PET studies of medicated patients with

schizophrenia has been confirmed in our laboratory[36] and in other laboratories.[37]

Statistical Analysis

Shapiro-Wilk tests were conducted to examine the distribution of variables. Clinico-demographic characteristics and $D_{2/3}R$ occupancy were compared between subjects with and without hyperprolactinemia at the baseline PET visit and the postreduction PET visit by Fisher exact tests or Mann-Whitney tests for categorical or continuous variables, respectively. Prolactin levels were compared between the baseline PET visit and the postreduction PET visit by Wilcoxon signed rank tests.

Stepwise linear regression analyses were performed to examine the effects of the following variables on prolactin levels: age, gender, antipsychotics (olanzapine or risperidone), $D_{2/3}R$ occupancy, and other characteristics that were significantly different between those with and without hyperprolactinemia. Further, a logistic regression was performed to examine the effects of those characteristics of subjects, which were adopted in the stepwise linear regression analyses, on the likelihood that subjects had hyperprolactinemia. The same analyses were also conducted for prolactin unit levels. In addition, as an exploratory analysis, we performed Mann-Whitney tests with the last-observation-carried-forward (LOCF) method to compare the prolactin levels at the baseline PET visit and at the postreduction PET visit between those with clinical deterioration throughout this study and those without. Lastly, to evaluate the $D_{2/3}R$ occupancy threshold for hyperprolactinemia in this population, we calculated the sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) with increments of 1% between 60% and 70% in $D_{2/3}R$ occupancy. Fisher exact tests were also employed at each cutoff level to assess the relationship between hyperprolactinemia and $D_{2/3}R$ occupancy. The same analyses were conducted stratified by antipsychotic.

Statistical analyses were carried out using IBM SPSS Statistics, version 20 (IBM Corp, Armonk, New York). A 2-sided P value of less than .05 was considered statistically significant for all tests; however, regarding the comparisons of clinico-demographic characteristics between those with and without hyperprolactinemia, tests with an associated P value less than .0016 (.05/30) are considered significant, owing to the number of the comparisons. Continuous variables are described as mean ± SD (range).

RESULTS

Subjects

Forty-two subjects participated in this study. Demographic and clinical characteristics of the subjects at the baseline PET scan visit are summarized in Table 1. Subjects were mainly white, aged about 60 years. Three-fourths of the subjects were male, and more than half of the subjects were taking olanzapine. They mostly suffered from early-onset schizophrenia with modest illness severity. Thirty-nine subjects (92.9%) completed both PET scans. The characteristics at the postreduction PET visit are summarized in Supplementary eTable 1. Seven subjects experienced clinical deterioration throughout the study. One subject was excluded from the analysis because of a brain anomaly. Thus, we analyzed data consisting of 79 (= [42–1] + [39–1]) pairs of $D_{2/3}R$ occupancy and prolactin levels (Figure 1). There were 16 subjects (39.0%) and 11 subjects (28.9%) who showed hyperprolactinemia at baseline and at postreduction PET visits, respectively. Prolactin levels decreased after dose reduction of antipsychotics (from 24.1 ± 30.2 [5.0–183.0] ng/mL to 17.2 ± 15.1 [2.0–77.0] ng/mL, $Z = -4.26$, $P < .001$). $D_{2/3}R$ occupancy decreased after dose reduction (from 70.4% ± 11.9% [40.6%–91.2%] to 65.0% ± 13.0% [27.9%–84.7%], $Z = -3.87$, $P < .001$). The other clinico-demographic characteristics before and after the dose reduction were previously reported.[24] The ratio of risperidone intake was higher in subjects with hyperprolactinemia than in those without hyperprolactinemia at the baseline PET visit ($df = 1$, $P < .001$). No differences were found in the prolactin levels between those with clinical deterioration and those without clinical deterioration at both baseline and postreduction PET visits.

Predicting Prolactin Levels With $D_{2/3}R$ Occupancy in Older Patients With Schizophrenia

The main predictor of prolactin levels was female gender (β = 0.32, $P = .006$, vs male). Other predictors were antipsychotics (β = 0.23, $P = .02$, risperidone vs olanzapine) and $D_{2/3}R$ occupancy (β = 0.23, $P = .04$). This model accounted for 28.3% (adjusted R^2) of the total variance ($F_{3,75} = 11.27$ and $P < .001$). Furthermore, the main predictor of prolactin unit levels was antipsychotics (β = 0.28, $P = .007$, risperidone vs olanzapine). The other predictor was $D_{2/3}R$ occupancy (β = 0.26, $P = .03$). This model accounted for 24.9% (adjusted R^2) of the total variance ($F_{3,75} = 9.60$ and $P < .001$).

Predicting Hyperprolactinemia With $D_{2/3}R$ Occupancy in Older Patients With Schizophrenia

The logistic regression analysis showed significant results ($\chi^2_4 = 29.13$, $P < .001$). The model explained 42.7% (Nagelkerke R^2) of the variance in hyperprolactinemia and correctly classified 78.5% of cases. Sensitivity, specificity, PPV, and NPV were 59.3%, 88.5%, 72.7%, and 80.7%, respectively. The only predictor was antipsychotics (β = 2.56, $P < .001$). Risperidone had 12.87 times higher odds to exhibit hyperprolactinemia than olanzapine.

$D_{2/3}R$ Occupancy Threshold for Hyperprolactinemia in Older Patients With Schizophrenia

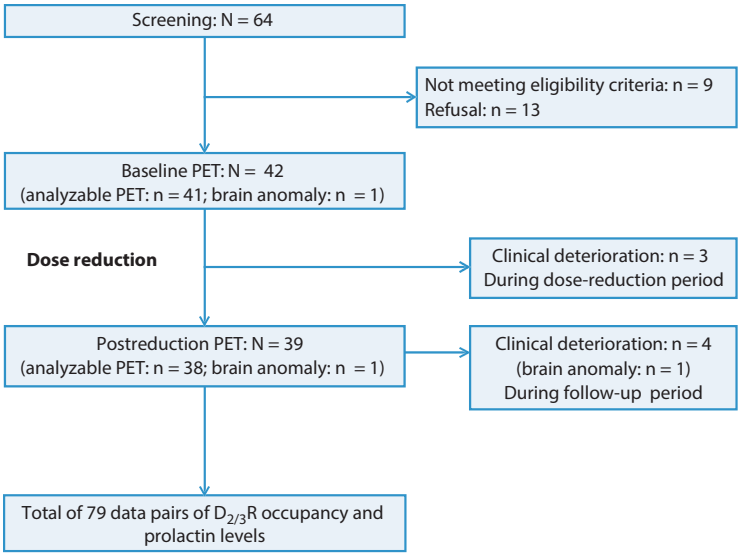
The reliability measures for hyperprolactinemia at each cutoff point of $D_{2/3}R$ occupancy are presented in Table 2. The cutoff point of 66% resulted in highest sensitivity and specificity (0.44 and 0.81, respectively). PPV and NPV at this cutoff point were 0.78 and 0.48, respectively. Those with

Table 1. Characteristics of Subjects at Baseline PET Visit

	Total (N = 41)	With Hyperprolactinemia (n = 16)	Without Hyperprolactinemia (n = 25)	Mann-Whitney Test		Fisher Exact Test	
				Z Score	*P* Value	*df*	*P* Value
Age, y	60.2 ± 6.7 (50–79)	59.0 ± 6.8 (50–71)	61.0 ± 6.6 (51–79)	−0.87	.38		
Female, n (%)	11 (26.8)	8 (50.0)	3 (12.0)			1	.007
African, n (%)	4 (9.8)	1 (6.3)	3 (12.0)			1	.38
Asian, n (%)	2 (4.9)	0 (0)	2 (8.0)			1	.51
White, n (%)	35 (85.4)	15 (93.8)	20 (80.0)			1	1.00
Schizophrenia, n (%)	33 (80.5)	14 (87.5)	19 (76.0)			1	.45
Schizoaffective, n (%)	8 (19.5)	2 (12.5)	6 (24.0)			1	.45
Age at onset, y	25.1 ± 9.7 (7–48)	26.1 ± 10.2 (13–48)	24.4 ± 9.5 (7–46)	−0.51	.61		
Duration of illness, y	34.3 ± 10.6 (8–55)	33.1 ± 13.0 (8–55)	35.0 ± 9.0 (13–50)	−0.46	.65		
No. of episodes	5.7 ± 4.8 (1–20)	5.6 ± 4.5 (1–18)	5.8 ± 5.1 (2–20)	−0.03	.98		
No. of hospitalizations	5.9 ± 5.4 (0–20)	5.0 ± 4.5 (0–18)	6.5 ± 5.9 (0–20)	−0.66	.51		
Years of antipsychotic exposure	30.0 ± 11.7 (4–55)	30.8 ± 12.2 (8–55)	29.4 ± 11.5 (4–50)	−0.28	.78		
PANSS total score	60.2 ± 13.5 (30–82)	54.4 ± 15.3 (30–82)	63.9 ± 11.0 (37–78)	−2.19	.03		
Positive subscale score	12.8 ± 3.9 (7–20)	10.9 ± 3.8 (7–18)	14.0 ± 3.5 (8–20)	−2.53	.01		
Negative subscale score	17.9 ± 5.0 (7–28)	16.8 ± 5.3 (7–24)	18.6 ± 4.8 (10–28)	−0.93	.36		
General psychopathology subscale score	29.5 ± 6.8 (16–43)	26.8 ± 7.4 (16–43)	31.3 ± 5.9 (17–39)	−2.16	.03		
BPRS total score	41.3 ± 8.7 (24–58)	37.0 ± 8.9 (24–55)	44.0 ± 7.6 (26–58)	−2.60	.009		
AIMS total score	1.4 ± 2.4 (0–10)	1.8 ± 2.9 (0–9)	1.2 ± 2.1 (0–10)	−0.03	.98		
BAS total score	0.7 ± 1.5 (0–6)	0.9 ± 1.5 (0–5)	0.5 ± 1.4 (0–6)	−1.42	.16		
SAS total score	3.2 ± 2.6 (0–11)	3.8 ± 3.1 (0–11)	2.8 ± 2.3 (0–8)	−0.76	.45		
SWN total score	92.0 ± 15.6 (64–117)	95.0 ± 18.2 (64–117)	90.0 ± 13.5 (68–114)	−0.98	.33		
Olanzapine, n (%)	24 (58.5)	4 (25.0)	20 (80.0)			1	**< .001**[b]
Daily dose, mg	20.6 ± 6.7 (10–35)	23.8 ± 7.5 (15–30)	20.0 ± 6.5 (10–35)	−0.99	.32		
Risperidone, n (%)	17 (41.5)	12 (75.0)	5 (20.0)				
Daily dose, mg	4.3 ± 2.5 (2–12)	4.0 ± 1.7 (2–6)	5.0 ± 4.0 (2–12)	−0.05	.96		
Chlorpromazine equivalent dose, mg	419.5 ± 186.4 (200–1200)	418.8 ± 160.1 (200–600)	420.0 ± 204.6 (200–1200)	−0.34	.73		
$D_{2/3}R$ occupancy, %	70.4 ± 11.9 (40.6–91.2)	74.5 ± 13.1 (40.6–91.2)	67.7 ± 10.5 (47.5–82.7)	−1.90	.06		
Prolactin level, ng/mL							
Total	24.1 ± 30.2 (5–183)	44.9 ± 40.6 (19–183)	10.8 ± 4.1 (5–22)	−5.31	**< .001**[c]		
Female	14.8 ± 8.6 (5–39)	26.9 ± 6.2 (19–39)	10.4 ± 3.6 (5–17)	−4.14	.01		
Male	49.5 ± 49.5 (9–183)	62.9 ± 52.4 (25–183)	14.0 ± 7.0 (9–22)	−2.45	**< .001**[c]		
Prolactin unit, U[d]	1.1 ± 1.2 (0.27–7.56)	2.0 ± 1.6 (1.01–7.56)	0.6 ± 0.2 (0.27–0.91)	−5.35	**< .001**[c]		
Hyperprolactinemia, n (%)	16 (39.0)	16 (100.0)	0 (0.0)				

[a]Values are mean ± SD (range) unless otherwise noted.
[b]The ratio of risperidone intake was higher in subjects with hyperprolactinemia.
[c]Prolactin levels were higher in subjects with hyperprolactinemia.
[d]Prolactin unit levels (U) were calculated by dividing prolactin levels (ng/mL) by the threshold of hyperprolactinemia for each gender (ie, > 18.77 ng/mL and > 24.20 ng/mL for male and female, respectively).
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, $D_{2/3}R$ = dopamine $D_{2/3}$ receptor, PANSS = Positive and Negative Syndrome Scale, PET = positron emission tomography, SAS = Simpson-Angus Scale, SD = standard deviation, SWN = Subjective Well-Being Under Neuroleptic Treatment Scale.

Figure 1. Flow Diagram



Abbreviations: $D_{2/3}R$ = dopamine $D_{2/3}$ receptor, PET = positron emission tomography.

$D_{2/3}R$ occupancy of 66% or higher were more likely to have hyperprolactinemia than those with lower occupancy ($P = .03$).

When each antipsychotic was considered separately, the cutoff point for hyperprolactinemia was 66% for olanzapine ($P = .04$). Sensitivity, specificity, PPV, and NPV for olanzapine were 100.0%, 23.3%, 42.5%, and 100.0%, respectively, at the cutoff point. Highest sensitivity and specificity were also observed at the cutoff point of 66% for risperidone with a trend-level significance ($P = .07$). Sensitivity, specificity, PPV, and NPV for risperidone were 57.1%, 77.8%, 66.7%, and 70.0%, respectively.

DISCUSSION

To our knowledge, this is the first study to examine the relationship between the striatal $D_{2/3}R$ occupancy and prolactin levels in older

Table 2. Sensitivity, Specificity, PPV, and NPV in a Series of Cutoff Points of $D_{2/3}R$ Occupancy for Hyperprolactinemia[a]

Cutoff Point (%)	*P* Value	Sensitivity	Specificity	PPV	NPV
60	.29	0.38	0.76	0.81	0.31
61	.31	0.38	0.75	0.78	0.35
62	.22	0.39	0.76	0.78	0.37
63	.22	0.39	0.76	0.78	0.37
64	.09	0.41	0.79	0.78	0.42
65	.08	0.42	0.79	0.78	0.44
66	**.03**	**0.44**	**0.81**	**0.78**	**0.48**
67	.15	0.42	0.75	0.67	0.52
68	.10	0.44	0.76	0.67	0.56
69	.10	0.44	0.75	0.63	0.58
70	.17	0.42	0.73	0.59	0.58

[a]Sensitivity and specificity were greatest at the cutoff point of 66%, and Fisher exact test showed the significant differences in the ratio of hyperprolactinemia ($P = .03$).

Abbreviations: $D_{2/3}R$ = dopamine $D_{2/3}$ receptor, NPV = negative predictive value, PPV = positive predictive value.

patients with schizophrenia, extending the age range of previous studies of younger patients that reported on the relationship between striatal $D_{2/3}R$ occupancy and prolactin levels. We found that $D_{2/3}R$ occupancy predicted prolactin levels and prolactin unit levels in older patients with schizophrenia. The $D_{2/3}R$ occupancy threshold for hyperprolactinemia in our sample was 66%, which is lower than that reported for younger patients.[19,38] In a study of first-episode patients treated with haloperidol, Kapur et al[38] demonstrated that the likelihood of hyperprolactinemia increased as the striatal $D_{2/3}R$ occupancy exceeded 72%. Similarly, Tsuboi et al[19] reported that the estimated D_2R occupancy threshold for hyperprolactinemia was 73% in patients with chronic schizophrenia treated with olanzapine, risperidone, or ziprasidone. In our study, dividing the subjects by antipsychotic, we found that the cutoff points for hyperprolactinemia were 66% for both olanzapine and risperidone, which is lower than the 77% for olanzapine and 68% to 70% for risperidone that was found in a previous study.[19] Therefore, our finding suggests that the $D_{2/3}R$ occupancy threshold for antipsychotic-induced hyperprolactinemia may be lower in older patients than in younger patients.

Because all of the antipsychotics on market to date share the common property of blocking $D_{2/3}R$, the lower $D_{2/3}R$ occupancy threshold for hyperprolactinemia may be attributable to age-related decreases in $D_{2/3}R$ availability. Several in vivo PET imaging studies suggest that striatal $D_{2/3}R$ availability decreases with age in healthy individuals[22] as well as in patients with schizophrenia.[21,39,40] For example, Talvik et al[39] found that striatal $D_{2/3}R$ availability decreased by 7% to 8% per decade in antipsychotic-naive younger subjects. Wong et al[20] also observed similar age-related decreases in caudal $D_{2/3}R$ availability (8% to 9%) between antipsychotic-naive subjects and healthy controls. Similarly, Nordström et al[21] found that age-dependent decreases in putamen-to-cerebellum ratios did not differ between antipsychotic-naive younger patients and healthy controls. Moreover, we also found no differences in striatal $D_{2/3}R$ availability between antipsychotic-free older patients and healthy controls.[40] Taken together, these findings indicate that striatal $D_{2/3}R$ availability decreases with age in patients with schizophrenia in a magnitude similar to that in healthy controls, which may explain the lower striatal $D_{2/3}R$ occupancy threshold for hyperprolactinemia in older patients.

We found that female gender was a stronger predictor of prolactin levels than male gender, which has been a well-replicated finding in the literature.[41–44] Estrogen increases the number of lactotrophic cells of the anterior pituitary and acts on the hypothalamus to decrease dopaminergic neurotransmission.[41] Thus, hypersensitivity to prolactin elevation in females can be explained by the ability of estrogen to elevate serum prolactin levels and enhance responsiveness to prolactin-releasing stimuli such as antipsychotics.[41,45]

Our study also demonstrated a stronger association between risperidone and prolactin levels as compared with olanzapine, which is also a well-established finding.[44] The higher risk of hyperprolactinemia of risperidone was partly attributable to the fact that risperidone has relatively higher affinity to $D_{2/3}R$ than olanzapine.[46] This finding is in keeping with a previous finding by Tsuboi et al[19] that the estimated $D_{2/3}R$ occupancy threshold of hyperprolactinemia for risperidone (68% to 70%) was lower than that for olanzapine (77%). Also, another line of evidence suggests that the blood-brain barrier permeability of antipsychotics may influence the risk of hyperprolactinemia.[18] Arakawa et al[18] showed that the drug level ratio in the brain compared to plasma is higher in olanzapine than for risperidone. Thus, clinicians are advised to pay attention to hyperprolactinemia in female patients taking antipsychotics, especially risperidone.

The present study has to be interpreted in the light of several limitations. First, the sample size was only 41 subjects; however, our sample size is still larger than samples in previous PET studies. Second, only subjects treated with olanzapine and risperidone and less than 80 years of age were included in our study. Also, subjects' age range was considerably wide (from 50 to 79 years), with skewed distribution of race and ethnicity due to lack of minorities. Further research is needed in a sample consisting of a larger number of subjects, including older age groups and various racial and ethnic groups and those treated with different antipsychotics. Third, we did not explore $D_{2/3}R$ occupancy in the pituitary gland, where Arakawa et al[18] reported the positive correlation between $D_{2/3}R$ occupancy and prolactin levels. The differential disposition of antipsychotics across the blood-brain barrier might result in the difference in $D_{2/3}R$ occupancy between the pituitary gland and the striatum.[16] Fourth, the effects of genetic variants were not explored. It was noted that the dopamine D_2 receptor gene (*DRD2*) variants are linked with antipsychotic-induced hyperprolactinemia. For example, Taq1A variants in the *DRD2* are related to the risk of hyperprolactinemia in patients with schizophrenia.[47,48] Finally, this is a post hoc analysis of a previous PET study[24–26] that examined the effects of antipsychotic dose reduction in older patients with schizophrenia.

In conclusion, this is the first PET study to demonstrate that the striatal $D_{2/3}R$ occupancy is a strong predictor of prolactin levels in older patients with schizophrenia and that the $D_{2/3}R$ occupancy threshold for hyperprolactinemia is 66% in this population, which is lower than that reported in younger patients. Our previous study[24] suggested that the lowest $D_{2/3}R$ occupancy associated with clinical stability was at least 50% in older patients with schizophrenia. Given that the threshold of $D_{2/3}R$ occupancy for hyperprolactinemia was 66% in this population, the therapeutic window of $D_{2/3}R$ occupancy is proposed to be between 50% and 66% to achieve optimal therapeutic response. However, measuring $D_{2/3}R$ occupancy with PET for clinical purposes is not feasible owing to availability and cost. Our previous study[26] demonstrated the reliability of the hyperbole saturation equation in estimating $D_{2/3}R$ occupancy with olanzapine and risperidone using blood concentrations of the drugs. This model will help to target an individual-specific antipsychotic dose that both achieves therapeutic efficacy and minimizes adverse effects. Finally, clinicians are advised to regularly monitor prolactin levels and try to minimize exposure to antipsychotics while maintaining their clinical effectiveness in stable older patients with schizophrenia.

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Drug names: olanzapine (Zyprexa and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Helen Lavretsky, MD, MS, at hlavretsky@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY
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Supplementary Material

Article Title: Threshold of Dopamine $D_{2/3}$ Receptor Occupancy for Hyperprolactinemia in Older Patients With Schizophrenia

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DOI Number: 10.4088/JCP.15m10538

List of Supplementary Material for the article

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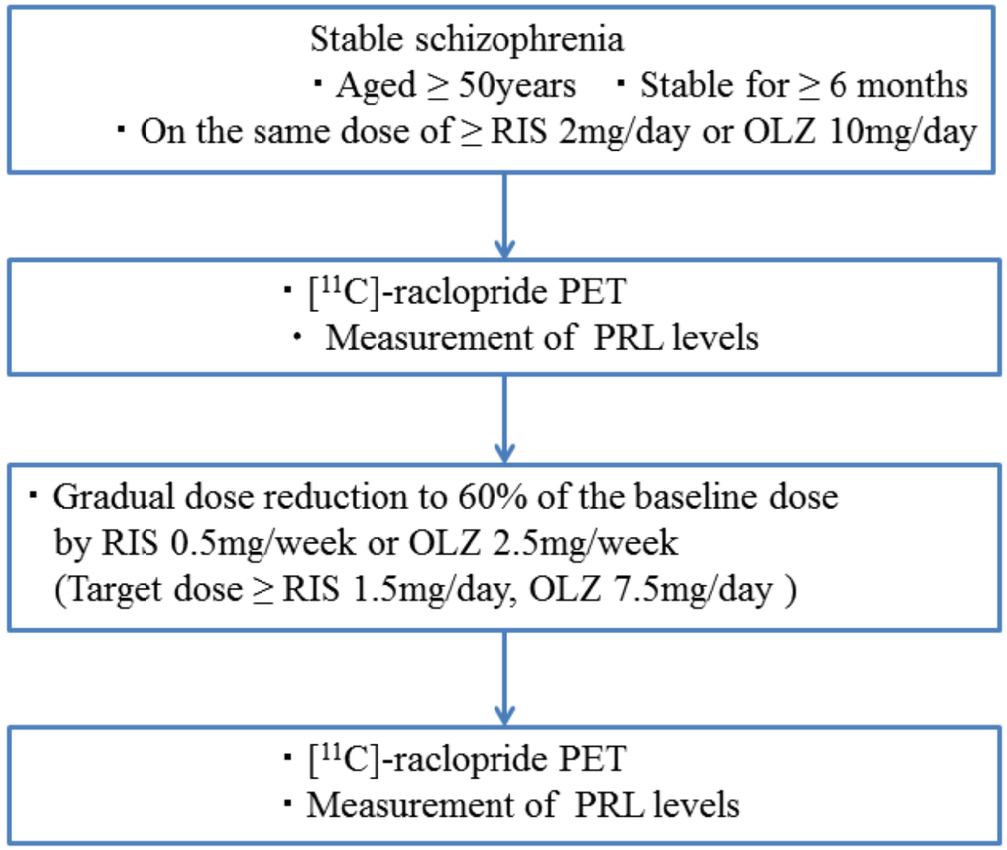
Supplementary eFigure 1. Study overview



This study included clinically stable subjects with older schizophrenia who were on the same dose of RIS or OLZ for 6-12 months. Subjects were assessed using clinical scales on symptomatology and received a [^{11}C]-raclopride PET scan to determine the baseline $D_{2/3}R$ occupancy. Venous blood was collected before the PET scan for the measurement of PRL levels. Then, subjects underwent a gradual dose reduction of up to 40% of their baseline dose. At least two weeks after reaching the target dose, the post-reduction [^{11}C]-raclopride PET scan was performed. Another venous blood was taken before the PET scan.

Abbreviations: $D_{2/3}R$, dopamine $D_{2/3}$ receptor; OLZ, olanzapine; PET, positron emission tomography; PRL, prolactin; RIS, risperidone

Supplementary eTable 1.

Characteristics of subjects at post-reduction PET visit

	Total (n = 38)	Hyperprolactinemia (+) (n = 11)	Hyperprolactinemia (-) (n = 27)	Mann-Whitney Test		Fisher's Exact Test	
	Mean ± SD (range) or n (%)	Mean ± SD (range) or n (%)	Mean ± SD (range) or n (%)	Z score	P value	df	P value
Age in years	60.3 ± 6.9 (50 - 79)	57.9 ± 6.3 (50 - 68)	61.3 ± 7.0 (50 - 79)	-1.34	0.18		
Female	11 (28.9)	5 (45.5)	6 (22.2)			1	0.24
African	4 (10.5)	1 (9.1)	3 (11.1)			1	0.65
Asian	2 (5.3)	0 (0)	2 (7.4)			1	1.00
Caucasian	32 (84.2)	10 (90.9)	22 (81.5)			1	1.00
Schizophrenia	31 (81.6)	9 (81.8)	22 (81.5)			1	1.00
Schizoaffective	7 (18.4)	2 (18.2)	5 (18.5)			1	1.00
Age of onset in years	26.1 ± 9.3 (13 - 48)	25.9 ± 11.9 (13 - 48)	26.1 ± 8.4 (16 - 46)	-0.50	0.62		
Duration of illness in years	33.7 ± 10.8 (8 - 55)	32.3 ± 15.5 (8 - 55)	34.2 ± 8.5 (15 - 50)	-0.24	0.81		
Number of episodes	5.8 ± 5.0 (1 - 20)	6.5 ± 5.2 (1 - 18)	5.6 ± 4.9 (2 - 20)	-0.41	0.68		
Number of hospitalizations	5.7 ± 5.2 (0 - 20)	5.4 ± 5.6 (0 - 18)	5.9 ± 5.2 (1 - 20)	-0.55	0.58		
Years of antipsychotic exposure	29.2 ± 11.7 (4 - 55)	29.2 ± 14.5 (8 - 55)	29.1 ± 10.7 (4 - 50)	-0.10	0.92		
PANSS total score	59.0 ± 14.0 (30 - 79)	52.5 ± 16.8 (30 - 79)	61.6 ± 12.2 (36 - 78)	-1.53	0.13		
Positive subscale score	12.7 ± 4.0 (7 - 22)	10.9 ± 4.3 (7 - 18)	13.4 ± 3.7 (7 - 22)	-1.72	0.09		
Negative subscale score	17.3 ± 5.3 (7 - 28)	15.7 ± 5.5 (7 - 23)	18.0 ± 5.2 (9 - 28)	-1.05	0.29		
General psychopathology subscale score	29.0 ± 6.7 (16 - 39)	25.9 ± 7.7 (16 - 39)	30.3 ± 6.0 (17 - 39)	-1.60	0.11		
BPRS total score	40.8 ± 8.9 (24 - 62)	36.4 ± 9.6 (24 - 51)	42.7 ± 8.1 (25 - 62)	-1.84	0.07		
AIMS total score	1.3 ± 2.3 (0 - 9)	1.5 ± 2.1 (0 - 7)	1.3 ± 2.3 (0 - 9)	-0.45	0.65		
BAS total score	0.2 ± 0.8 (0 - 4)	0.4 ± 0.9 (0 - 3)	0.2 ± 0.8 (0 - 4)	-0.94	0.35		
SAS total score	1.8 ± 1.8 (0 - 8)	1.1 ± 1.2 (0 - 3)	2.1 ± 2.0 (0 - 8)	-1.61	0.11		
SWN total score	93.0 ± 17.2 (52 - 119)	95.4 ± 22.5 (52 - 118)	92.0 ± 14.9 (67 - 119)	-0.98	0.33		
OLZ	23 (60.5)	3 (27.3)	20 (74.1)			1	0.01

Daily dose, mg	13.4 ± 4.4 (7.5 - 22.5)	10.8 ± 1.4 (10.0 - 12.5)	13.8 ± 4.6 (7.5 - 22.5)	-0.06	0.95
RIS	15 (39.5)	8 (72.7)	7 (25.9)		
Daily dose, mg	2.9 ± 1.6 (1.5 - 7.5)	2.8 ± 1.1 (1.5 – 4.0)	3.1 ± 2.1 (1.5 - 7.5)	-1.08	0.28
CPZ equivalent dose, mg	277.6 ± 118.9 (150 - 750)	259.1 ± 97.0 (150 - 400)	285.2 ± 127.7 (150 - 750)	-0.59	0.55
$D_{2/3}R$ occupancy, %	65.0 ± 13.0 (27.9 - 84.7)	69.2 ± 13.2 (50.7 - 84.7)	63.3 ± 12.8 (27.9 - 81.1)	-1.24	0.22
PRL level, ng/mL					
Total	17.2 ± 15.1 (2 - 77)	34.3 ± 17.8 (19 - 77)	10.2 ± 5.3 (2 - 21)	-4.63	< **0.001** [a]
Female	12.2 ± 7.5 (2 - 33)	22.8 ± 5.3 (19 - 33)	9.1 ± 4.7 (2 - 18)	-3.68	0.006
Male	29.4 ± 21.7 (5 - 77)	48.0 ± 18.1 (30 - 77)	13.8 ± 6.4 (5 - 21)	-2.74	0.002
PRL unit, U	0.8 ± 0.6 (0.11 - 3.18)	1.6 ± 0.7 (1.01 - 3.18)	0.5 ± 0.3 (0.11 - 0.96)	-4.78	< **0.001** [e]
Hyperprolactinemia	11 (28.9)	11 (100.0)	0 (0)		

PRL unit levels [U] were calculated by dividing PRL levels [ng/mL] by the threshold of hyperprolactinemia for each gender (i.e. >18.77 ng/mL and >24.20 ng/mL for make and female, respectively).

Abbreviations: AIMS, The Abnormal Involuntary Movement Scale; BAS, The Barnes Rating Scale for Drug-Induced Akathisia; BPRS, The Brief Psychiatric Rating Scale; CPZ, chlorpromazine equivalent dose; D2/3R, dopamine D2/3 receptor; OLZ, olanzapine; PANSS, The Positive and Negative Syndromes Scale; PET, positron emission tomography; PRL, prolactin; RIS, risperidone; SAS, The Simpson-Angus Scale; SD, standard deviation; SWN, The Subjective Well-being on Neuroleptic Medications

a, b, Prolactin levels were higher in the subjects with hyperprolactinemia.