Evaluation of Antipsychotic Dose Reduction in Late-Life Schizophrenia: A Prospective Dopamine D2/3 Receptor Occupancy Study

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**IMPORTANCE** Patients with late-life schizophrenia (LLS) are highly susceptible to antipsychotic adverse effects. Treatment guidelines endorse lower antipsychotic doses. However, the optimal dose of antipsychotics and associated dopamine D2/3 receptor (D2/3R) occupancies remain largely unexplored in patients with LLS.

**OBJECTIVE** To evaluate effects of antipsychotic dose reduction on striatal dopamine D2/3R occupancies, clinical variables, and blood pharmacokinetic measures in patients with LLS.

**DESIGN, SETTING, AND PARTICIPANTS** An open-label, single-arm prospective study with a 3- to 6-month follow-up period (January 10, 2007, to October 21, 2013) was conducted at an academic tertiary care center with practice for ambulatory care. Participants included 35 outpatients with clinically stable LLS (patients aged ≥50 years receiving olanzapine or risperidone monotherapy at the same dose for 6 to 12 months). Follow-up was completed on October 21, 2013, and analysis was conducted from October 22, 2014, to February 2, 2015.

**INTERVENTIONS** Carbon 11–labeled raclopride positron emission tomography, clinical measures, and blood pharmacokinetic measures performed before and after gradual dose reduction by up to 40% from the baseline dose and at least 3 months after dose reduction.

**MAIN OUTCOMES AND MEASURES** Striatal dopamine D2/3R occupancies with antipsychotics, clinical measures (Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale, Targeted Inventory on Problems in Schizophrenia, Simpson-Angus Scale, Barnes Rating Scale for Drug-Induced Akathisia, Udvalg for Kliniske Undersøgelser Side Effect Rating Scale), and blood pharmacokinetic measures (prolactin and antipsychotic blood levels).

**RESULTS** Dopamine D2/3R occupancy of the entire sample decreased by a mean (SD) of 6.2% (8.2%) following dose reduction (from 70% [12%] to 64% [12%; P < .001). The lowest D2/3R occupancy associated with clinical stability was 50%. Extrapyramidal symptoms (EPSs) were more likely to occur with D2/3R occupancies higher than 60%: 90.5% (19 of 21) of the participants with baseline EPSs and 76.9% (10 of 13) of the participants with postreduction EPSs had striatal D2/3R occupancies higher than 60%. The baseline D2/3R occupancies were lower in patients with clinical deterioration (n = 5) than in those whose condition remained stable (n = 29) (58% [15%] vs 72% [10%; P = .03). Following dose reduction, Targeted Inventory on Problems in Schizophrenia score increased (P = .046) and Positive and Negative Syndrome Scale (P = .02), Brief Psychiatric Rating Scale (P = .03), Simpson-Angus Scale (P < .001), Barnes Rating Scale for Drug-Induced Akathisia (P = .03), and Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (P < .001) scores and prolactin (P < .001) and blood antipsychotic (olanzapine, P < .001; risperidone plus the metabolite 9-hydroxyrisperidone, P = .02) levels all decreased.

**CONCLUSIONS AND RELEVANCE** Antipsychotic dose reduction is feasible in patients with stable LLS, decreasing adverse effects and improving illness severity measures. The results of the present study suggest a lower therapeutic window of D2/3R occupancy in patients with LLS (50%-60%) than previously reported in younger patients (65%-80%).
Schizophrenia is a life-long illness that typically requires maintenance antipsychotic treatment throughout an individual’s life. Older age is a risk factor for antipsychotic-induced adverse effects, including parkinsonism, tardive dyskinesias, falls, and metabolic syndrome. Clinical guidelines developed by expert consensus recommend the use of lower doses of antipsychotics in older patients with schizophrenia. However, empirical data on age-specific antipsychotic dosing are limited.

Positron emission tomography (PET) studies in younger patients with schizophrenia have demonstrated that striatal dopamine D2/3 receptor (D2/3R) occupancy above 65% is associated with good clinical response. Extrapyramidal symptoms (EPSs) are more likely to be observed with D2/3R occupancy above 80%. Thus, D2/3R occupancies of 65% to 80% define a therapeutic window that maximizes therapeutic benefits and minimizes adverse effects.

In the absence of similar data in patients with late-life schizophrenia (LLS), the present prospective PET study assessed D2/3R occupancy before and after reduction of the antipsychotic dose by up to 40% in patients with LLS whose condition had been clinically stable with risperidone or olanzapine therapy. The patients were monitored for 3 to 6 months after dose reduction. Our aims were to evaluate the effect of antipsychotic dose reduction on striatal dopamine D2/3R occupancies and determine the optimal therapeutic window of D2/3R occupancy in patients with LLS.

Methods

Overall Design
We recruited patients 50 years or older with clinically stable schizophrenia who had been receiving the same dose of risperidone or olanzapine for 6 to 12 months (26 patients for 12 months and 9 patients for 6 months) (Figure). Participants were assessed with clinical scales for symptoms and adverse effects at baseline. A carbon 11-labeled ([11C])-raclopride PET scan was performed to determine baseline antipsychotic D2/3R occupancy. Subsequently, participants underwent a gradual dose reduction of up to 40% of their baseline dose or to the lower limit of the recommended dosage range (ie, 7.5 mg/d for olanzapine and 1.5 mg/d for risperidone). Clinical assessments and a [11C]-raclopride PET scan were performed again at least 2 weeks after the final target dose was attained to ensure steady-state antipsychotic concentration in the brain. The participants were subsequently monitored for 3 to 6 months (26 patients for 6 months and 9 patients for 3 months) with clinical assessments. When participants developed clinical deterioration, the dose was increased until clinical stabilization was regained.

Setting and Participants
The study was approved by the Research Ethics Board at the Centre for Addiction and Mental Health, authorized by Health Canada, and registered at ClinicalTrials.gov (NCT00716755). All participants were recruited and provided written informed consent at the Centre for Addiction and Mental Health, Toronto, Ontario, between January 10, 2007, and October 21, 2013. Follow-up was completed on October 21, 2013, and analysis was conducted from October 22, 2014, to February 2, 2015. Individuals included in the study received financial compensation. Participants were outpatients 50 years or older with a diagnosis of either schizophrenia or schizoaffective disorder with early onset (ie, age at onset ≤50 years) as per the criteria of the Structured Clinical Interview for the DSM-IV. Participants were clinically stable, as determined by the following factors: no hospitalizations for 6 months; continuous treatment with oral antipsychotic monotherapy with either olanzapine or risperidone at a steady dosage of at least 10 mg/d or 2 mg/d, respectively; and a score of 3 or less on items of delusion, unusual thought content, and hallucinatory behavior on the Positive and Negative Syndrome Scale (PANSS). The participants were allowed to receive anxiolytics and antidepressants other than olanzapine or risperidone. Participants were excluded if they were not capable of providing informed consent as per the MacArthur Competence Assessment Tool for Clinical Research, had a history of treatment with a depot antipsychotic, met criteria for substance abuse or dependence within the past 6 months, had a positive urine screen result for substance abuse, had changed their dose of other psychotropics for mental health reasons within the past 6 months, or had an unstable medical condition.

Procedures

Clinical Assessments
Symptom severity and adverse effects were assessed at the baseline PET scan visit, at the follow-up PET scan visit, weekly between both PET scans (ie, dose reduction phase), and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 weeks after the follow-up PET scan (ie, follow-up phase). The assessments included the PANSS, Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression Scale–Severity, Functional Assessment for Comprehensive Treatment of Schizophrenia, and Targeted Inventory on Problems in Schizophrenia (TIP-Sz). The assessments for adverse effects included the Simpson-Angus Scale, Barnes Rating Scale for Drug-Induced Akathisia (BAS), Abnormal Involuntary Movement Scale, Subjective Well-being on Neuroleptic Medications, and Udvalg for Kliniske Undersøgelser Side Effect Rating Scale. The definition of EPSs included the presence of parkinsonism (a total Simpson-Angus Scale score of ≥3) or akathisia (a BAS global score of ≥2). Tardive dyskinesia was defined as an Abnormal Involuntary Movement Scale global severity score of 2 or more.

The PANSS, TIP-Sz, and Subjective Well-being on Neuroleptic Medications measures were performed at both PET scan visits and the final visit. The other scales were conducted at every visit.

Antipsychotic Dose Reduction or Titration
After the baseline PET scan, the antipsychotic dose was reduced by up to 40% of the baseline dosage, with a lower limit of 7.5 mg/d for olanzapine or 1.5 mg/d for risperidone based on published clinical guidelines. The dose was reduced weekly by 2.5 mg for olanzapine or 0.5 mg for risperidone; doses of all other psychotropics were maintained constant throughout the study. If participants demonstrated clinical deterioration (ie, an increase of ≥20% in the total BPRS score from base-
line), the antipsychotic dose was increased until clinical stabilization was achieved.

**Blood Sampling**
Venous blood samples were collected before each PET scan. Levels of risperidone, the metabolite 9-hydroxyrisperidone, and olanzapine were assayed in heparinized plasma using liquid chromatography with tandem mass spectrometry detection. Prolactin concentration was assayed using a chemiluminescent immunoassay (Prolactin 33530; Access Immunoassay System). Hyperprolactinemia was defined as a prolactin concentration greater than 18.77 μg/L for men and greater than 24.20 μg/L for women (to convert to nanomoles per liter, multiply by 43.478).23

**PET Image Acquisition and Analysis**
[^11C]-Raclopride PET scans were completed at baseline and at least 2 weeks after the antipsychotic target dose was reached. The time between PET scans was variable because the time for the second PET scan depended on the time required to complete the dose reduction. The PET scans were performed 14 to 16 hours after the last dose of the antipsychotic was given using high-resolution research tomography (Siemens Molecular Imaging) that measured radioactivity in 207 brain sections with a thickness of 1.2 mm each and an in-plane resolution of approximately 2.8 mm full width at half-maximum. The transmission scan was acquired immediately before the emission scan using a single-photon point source (137 Cs; half-life, 30.2 years; energy γ = 662 keV).

The radiosynthesis of[^11C]-raclopride has been described in detail elsewhere.24 After each participant was placed on the scanning bed, a custom-fitted thermoplastic mask (TrueScan Imaging) was made and then used during PET scans to decrease movement. A saline solution containing[^11C]-raclopride was injected as a bolus through an antecubital vein. The mean (SD) total mass injected, radioactivity dose, and specific activity of[^11C]-raclopride for the baseline and follow-up scans were 2.82 (2.08) μg and 2.98 (2.81) μg, 9.56 (0.77) mCi and 9.75 (0.78) mCi, and 1593.94 (701.30) mCi/μmol and 1609.63 (763.75) mCi/μmol, respectively, without any significant differences between the 2 PET scanning sessions (P = .65, P = .62, and P = .73, respectively). Emission data were acquired in list mode for 60 minutes, reconstructed by filtered-backprojection, and framed in 5 one-minute, 20 two-minute, and 3 five-minute frames.

Each participant underwent 3-dimensional, brain volume, T1-weighted magnetic resonance imaging (inversion time, 650 milliseconds; field of view, 23 cm; 256 × 256; slice thickness, 0.9 mm; flip angle, 8°) (performed in a GE Discovery MR750 3.0-T scanner; General Electric Medical Systems) to permit accurate delineation of the brain regions for data analysis. The region of interest (ROI)–based analysis for[^11C]-raclopride has been described in detail elsewhere.25 Briefly, time activity curves from ROIs were obtained from the dynamic PET images in native space with reference to each participant’s coregistered magnetic resonance image. The coregistration of each participant’s magnetic resonance image to PET space was done using the normalized mutual information algorithm26 as implemented in Statistical Parametric Mapping, version 2 (SPM2; Wellcome Department of Cognitive Neurology). The time activity curves were analyzed using the simplified reference tissue method,27 using the cerebellum as the reference region, to derive a quantitative estimate of binding: the binding potential relative to the nondisplaceable compartment (BPND) as defined by the consensus nomenclature for in vivo imaging of reversibly binding radioligands.28 The basis

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**Figure. Summary of Results**

<table>
<thead>
<tr>
<th>Patients screened for eligibility</th>
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<td>Did not meet eligibility criteria</td>
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<td>Refused</td>
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<table>
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<td>Clinical deterioration</td>
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<td>Restabilization</td>
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<td>Clinical follow-up for 12-14 wk</td>
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<tr>
<td>Successful dose reduction</td>
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<td>9</td>
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EPS+ indicates with extrapyramidal symptoms; EPS−, without EPS; and PET, positron emission tomography.
The BPND data from 10 antipsychotic-free participants with schizophrenia (mean [SD] age, 66.1 [11.5] years; range, 50-83 years; 4 women; duration of antipsychotic-free state, 12.5 [18.6] years) were used to estimate age- and sex-corrected measures of BPND for each ROI using a linear regression equation. These estimated BPND values were used to calculate each participant’s D2/3R occupancy in each ROI using the following equation:

\[ \text{D2/3R occupancy} = \left( \frac{(\text{BPND}_{\text{antipsychotic-free}} - \text{BPND}_{\text{drug}})}{(\text{BPND}_{\text{antipsychotic-free}} \times 100)} \right) \]

where \( \text{BPND}_{\text{antipsychotic-free}} \) is the age- and sex-corrected BPND derived from antipsychotic-free participants with schizophrenia, and \( \text{BPND}_{\text{drug}} \) is the BPND obtained from participants receiving oral risperidone or olanzapine.

### Statistical Analysis

Total or subscale scores in the clinical rating scales were analyzed by the generalized estimation equation for repeated measures to compare baseline and follow-up PET scan visits as well as the final visit. Linear or Poisson regression was used for continuous or discrete variables, respectively. Multiple comparisons were conducted with Bonferroni correction. Baseline and follow-up doses and plasma levels of antipsychotics and serum prolactin concentrations were compared using Wilcoxon signed rank tests. Baseline and follow-up D2/3R occupancies were compared by paired, 2-tailed t tests. Baseline and follow-up D2/3R occupancies were compared between participants with and without clinical deterioration during the follow-up phase and between participants with and without EPSs by Mann-Whitney tests or t tests based on their distribution.

Statistical significance was established at \( P < .05 \) (2-tailed).

### Results

#### Baseline Characteristics of Participants

The sample included at baseline was composed of 22 participants receiving olanzapine and 13 receiving risperidone. Detailed baseline demographic and clinical characteristics are summarized in Table 1 and Table 2.

#### Clinical Data After Dose Reduction

Clinical data on the sample at baseline and follow-up PET scan visits and at the final visit are presented in Table 2 and the Figure. The entire sample was composed of 35 participants, and 33 participants (94%) completed the dose reduction phase: 2 individuals developed clinical deterioration before dose reduction was completed. For the other 33 participants, the mean (SD) time to achieve the dose reduction was 2.0 (0.6) weeks, and the time between the 2 PET scans was 5.9 (0.4) weeks. Four of the 33 (12%) participants who completed the dose reduction experienced clinical deterioration during the follow-up phase. Among those with clinical deterioration, 5 participants achieved stabilization with an antipsychotic dose increase and 1 experienced symptomatic fluctuation (Figure). Overall, slight but significant symptomatic improvements were found in total scores in the PANSS, BPRS, and TIP-Sz following the dose reduction (\( P = .02 \), \( P = .03 \), and \( P = .046 \), respectively). Participants with clinical deterioration were associated with younger age at onset (18.7 [7.8]; range, 19-31 years vs 27.5 [8.6]; range, 16-46 years; \( t_{33} = 2.33; P = .03 \)) and greater number of hospitalizations (9.8 [5.8]; range, 4-15 vs 5.5 [5.1]; range, 0-20; \( U = 40.50; P = .04 \)), and lower follow-up serum prolactin concentrations (6.5 [1.9]; range, 4.0-8.0 μg/L vs 17.1 [14.4]; range, 2.0-77.0 μg/L; \( U = 21.50; P = .04 \)); (eTable 1 in the Supplement).
Dopamine D2/3R Occupancies and Clinical Symptoms

Striatal D2/3R occupancies and clinical outcomes are summarized in Table 2 and in eTable 2 and eFigure 1 in the Supplement. Baseline D2/3R occupancy was 70% (12%) (range, 41%-89%) (Table 2) in the striatum (mean putamen, caudate, and ventral striatum occupancies). One participant who presented with clinical deterioration was not included in the PET analysis because an incidental brain anomaly was found.

The mean (SD) striatal D2/3R occupancy of the 29 participants whose condition remained stable during the follow-up phase decreased from 72% (10%) (range, 47%-88%) to 66% (10%) (range, 49%-84%) (t28 = 3.84; P = .001). The baseline D2/3R occupancies were lower in the 5 participants with clinical deterioration (eTable 3 in the Supplement) than in the 29 who remained stable (58 [15%]; range, 41%-83% vs 72% [10%]; range, 47%-88%; U = 27.50; P = .001). The D2/3R occupancy was not different between participants with vs those without EPSs (eTable 4 in the Supplement).

Discussion

The present longitudinal PET study was designed to determine the minimal antipsychotic dose and D2/3R occupancy re-
required to maintain clinical wellness in patients with LLS. The results confirm and extend those of a pilot study report 20 showing that the antipsychotic dose can be successfully reduced in more than 80% of patients with stable LLS. The mean D₂/₃R occupancy of the entire sample decreased from 70% (12%) to 64% (12%) after a mean antipsychotic dose reduction of 34.6% (3.4%). Moreover, the dose reduction improved adverse effects, including EPSs and hyperprolactinemia, and unexpectedly improved clinical symptoms as assessed by the PANSS, BPRS, and TIP-Sz.

The mean striatal D₂/₃R occupancy was 64% after the dose reduction with 82.9% of participants showing clinical stability during the study. Nonetheless, the lowest observed striatal D₂/₃R occupancy was 50% in the participants who were clinically stable during the study. Moreover, 32 of 34 patients (94%) demonstrated a baseline striatal D₂/₃R occupancy higher than 50%, and all but 1 of the 29 participants (97%) who remained clinically stable showed a D₂/₃R occupancy higher than 50% post reduction. Baseline D₂/₃R occupancy was 40.6% and 57.4% in participants with clinical deterioration during the dose reduction phase, and follow-up D₂/₃R occupancy was 40.0%, 46.0%, and 80.9% in those with clinical deterioration during the follow-up phase (eTable 3 and eFigure 2 in the Supplement). Therefore, our results suggest that the lowest striatal D₂/₃R occupancy associated with clinical stability is at least 50% in patients with LLS, which is lower than the threshold previously reported for younger patients. 7–9 The design of our study restricted the dose reduction to 60% of the baseline dose or minimum of 1.5 mg/d for risperidone and 7.5 mg/d for olanzapine. Thus, it is possible that a lower threshold associated with clinical stability could be identified with exposure to lower antipsychotic doses than those allowed within the present study design.

Extrapyramidal symptoms were observed with striatal D₂/₃R occupancy as low as 40%. There was not a clear threshold of D₂/₃R occupancy for EPSs in the present study. These results are consistent with the fact that approximately 1 of 5 antipsychotic-naïve patients with schizophrenia experience spontaneous EPSs 22 and that aging is associated with increases in EPSs. 31 Still, striatal D₂/₃R occupancy higher than 60% seemed more likely to be associated with EPSs: 19 of 21 of the participants (90%) with baseline EPSs and 10 of 13 of the participants (77%) with postreduction EPSs had striatal D₂/₃R occupancies higher than 60%.

Participants with clinical deterioration were associated with younger age at onset, greater number of hospitalizations, lower baseline D₂/₃R occupancy, and lower serum prolactin concentrations during the follow-up. However, measuring D₂/₃R occupancy with PET for clinical purposes is not feasible owing to availability and cost. One report 34 described the reliability of the saturating hyperbole equation in estimating D₂/₃R occupancy with olanzapine and risperidone using blood concentrations of the drugs. eFigure 3 in the Supplement displays relationships between daily doses or plasma levels of antipsychotics and D₂/₃R occupancy in the striatum. The estimated plasma concentration of antipsychotics associated with D₂/₃R occupancy of 50% for risperidone was 6.5 ng/mL (95% CI, 3.0–10.0) and for olanzapine, 7.7 ng/mL (95% CI, 4.1–11.3), respectively. Thus, these values could be used to estimate D₂/₃R occupancy to identify individuals at risk of clinical deterioration following antipsychotic dose reduction. However, further research is needed to explore predictors of clinical deterioration following dose reduction in patients with schizophrenia.

This study should be considered in light of several limitations. We only enrolled outpatients aged 50 to 79 years who were receiving risperidone or olanzapine; the results cannot be generalized to other antipsychotics or to inpatients. Moreover, clinical follow-up was limited to 3 to 6 months, which is clearly too short to unequivocally confirm clinical stability. Previous longer-term, randomized clinical trials 35–37 of antipsychotic dose reduction have noted that relapse rates continue to gradually increase beyond 6 months, although the doses were reduced to 20% or less in those studies. Given that our study used an open-label, single-arm design, longer-term, double-blind, randomized clinical trials are warranted to compare clinical outcomes between dose reduction and dose maintenance groups in patients with LLS. Participants’ adherence to medication was examined by counting pills and by checking plasma levels. However, the possibility of suboptimal adherence cannot be ruled out, especially given the cognitive impairment associated with aging. 4–38,39

Conclusions

Our study demonstrates that antipsychotic dose reduction is feasible in most patients with stable LLS. Antipsychotic dose reduction can improve EPSs, hyperprolactinemia, and some symptoms through decreases in D₂/₃R occupancy. Our results also suggest that the striatal D₂/₃R occupancy threshold for antipsychotic therapeutic effects is lower (ie, 50%) in patients with LLS than in younger patients (65%), which has a significant implication on the management of this specific and ever-growing LLS population.
Antipsychotic Dose Reduction in Late-Life Schizophrenia

Original Investigation Research

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Statistical analysis: Pollock, Mamo.

Nakajima, Caravaggio, Suzuki, Uchida, Gerretsen, Mar, Mamo.

Administrative, technical, or material support: Graff-Guerrero, Nakajima, Suzuki, Uchida, Gerretsen, Mar, Pollock, Mamo.

Study supervision: Graff-Guerrero, Rajji, Nakajima, Mamo.

Conflict of Interest Disclosures: Dr Graff-Guerrero has received research support from the Canadian Institutes of Health Research (CIHR), US National Institutes of Health (NIH), Ontario Mental Health Foundation (OMHF), Brain and Behavior Research Foundation, Mexico Instituto de Ciencia y Tecnología del Distrito Federal and Consejo Nacional de Ciencia y Tecnología, and W. Garfield Weston Foundation. Dr Mulsant currently receives research funding from Brain Canada, the Centre for Addiction and Mental Health (CAMH) Foundation, the CIHR, and the US NIH. During the past 5 years, he received research support from Bristol-Myers Squibb, Eli-Lilly and Company, and Pfizer (all for medications used in NIH-funded clinical trials). He directly or indirectly owns stock of General Electric (<5%00). Dr Nakajima has received fellowship grants from the CIHR, Japan Society for the Promotion of Science, and Nakatomi Foundation and manuscript fees from Dainippon-Sumitomo Pharma and Kyowa Hakko Kirin. Dr Suzuki has received speaker or manuscript fees from Astellas Pharmaceutical, Dainippon-Sumitomo Pharma, Eli Lilly and Company, Elsevier Japan, Janssen Pharmaceutical, Otsuka Pharma, and Wely Japan. Dr Uchida has received grants from Astellas Pharmaceutical, Eisai, Otsuka Pharmaceutical, GlaxoSmithKline, Shionogi, Dainippon-Sumitomo Pharma, Eli Lilly and Company, Mochida Pharmaceutical, Meiji-Seika Pharma, and Yoshitomi Yakuhin and speakers honoraria from Otsuka Pharmaceutical, Eli Lilly and Company, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, AbbVie, MSD, and Janssen Pharmaceutical. Dr Gerretsen has received fellowship support from the CAMH Foundation, OMHF, and the CIHR Foundation. Dr Mamo has received investigator-initiated grant support from Pfizer. No other disclosures were reported.

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Previous Presentations: Some data from this study were presented at the 2013 Annual Meeting of the American Association for Geriatric Psychiatry; March 15, 2013; Los Angeles, California; the 2014 Annual Meeting of the Society of Biological Psychiatry; May 8, 2014; New York, New York; the 29th Collegium Internationale Neuro-Psychopharmacologicum; June 24, 2014; Vancouver, British Columbia, Canada; and the 53rd Annual Meeting of the American College of Neuropsychopharmacology; December 8, 2014; Phoenix, Arizona.

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REFERENCES


