

# Effects of Antipsychotic Medication on Brain Structure in Patients With Major Depressive Disorder and Psychotic Features

## Neuroimaging Findings in the Context of a Randomized Placebo-Controlled Clinical Trial

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**IMPORTANCE** Prescriptions for antipsychotic medications continue to increase across many brain disorders, including off-label use in children and elderly individuals. Concerning animal and uncontrolled human data suggest antipsychotics are associated with change in brain structure, but to our knowledge, there are no controlled human studies that have yet addressed this question.

**OBJECTIVE** To assess the effects of antipsychotics on brain structure in humans.

**DESIGN, SETTING, AND PARTICIPANTS** Prespecified secondary analysis of a double-blind, randomized, placebo-controlled trial over a 36-week period at 5 academic centers. All participants, aged 18 to 85 years, were recruited from the multicenter Study of the Pharmacotherapy of Psychotic Depression II (STOP-PD II). All participants had major depressive disorder with psychotic features (psychotic depression) and were prescribed olanzapine and sertraline for a period of 12 to 20 weeks, which included 8 weeks of remission of psychosis and remission/near remission of depression. Participants were then randomized to continue receiving this regimen or to be switched to placebo and sertraline for a subsequent 36-week period. Data were analyzed between October 2018 and February 2019.

**INTERVENTIONS** Those who consented to the imaging study completed a magnetic resonance imaging (MRI) scan at the time of randomization and a second MRI scan at the end of the 36-week period or at time of relapse.

**MAIN OUTCOMES AND MEASURES** The primary outcome measure was cortical thickness in gray matter and the secondary outcome measure was microstructural integrity of white matter.

**RESULTS** Eighty-eight participants (age range, 18-85 years) completed a baseline scan; 75 completed a follow-up scan, of which 72 (32 men and 40 women) were useable for final analyses. There was a significant treatment-group by time interaction in cortical thickness (left,  $t = 3.3$ ;  $P = .001$ ; right,  $t = 3.6$ ;  $P < .001$ ) but not surface area. No significant interaction was found for fractional anisotropy, but one for mean diffusivity of the white matter skeleton was present ( $t = -2.6$ ,  $P = .01$ ). When the analysis was restricted to those who sustained remission, exposure to olanzapine compared with placebo was associated with significant decreases in cortical thickness in the left hemisphere ( $\beta$  [SE], 0.04 [0.009];  $t_{34.4} = 4.7$ ;  $P < .001$ ), and the right hemisphere ( $\beta$  [SE], 0.03 [0.009];  $t_{35.1} = 3.6$ ;  $P < .001$ ). Post hoc analyses showed that those who relapsed receiving placebo experienced decreases in cortical thickness compared with those who sustained remission.

**CONCLUSIONS AND RELEVANCE** In this secondary analysis of a randomized clinical trial, antipsychotic medication was shown to change brain structure. This information is important for prescribing in psychiatric conditions where alternatives are present. However, adverse effects of relapse on brain structure support antipsychotic treatment during active illness.

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In their first few decades of use, antipsychotic medications were primarily administered to individuals with schizophrenia. With the introduction of atypical antipsychotics in the 1990s, evidence of efficacy led to the US Food and Drug Administration approval for use in mood disorders, including major depression, an illness with a lifetime prevalence of 10% to 15%.<sup>1</sup> Antipsychotics are also increasingly prescribed off label across the lifespan in a range of pediatric, adult, and geriatric disorders. For example, among all drug classes, antipsychotic medications are the ones most commonly prescribed in children with autism,<sup>2</sup> with nearly 20% receiving antipsychotic medication and rising.<sup>3</sup> Antipsychotics are also associated with sudden death,<sup>4</sup> with risk of unexpected death substantially higher in both children<sup>5</sup> and elderly individuals.<sup>6</sup>

With their increasing use, a better understanding of the risks and benefits of antipsychotics is important for prescribers, patients, and families. Focus has been on weighing the risk of metabolic adverse effects with the benefit of effectiveness in symptom management. Despite their risk, antipsychotics remain the foundation of treatment for schizophrenia, in part because it is believed that antipsychotics protect against the harmful effects of untreated psychosis on the brain.<sup>7</sup> However, data suggest that both older and newer antipsychotic medications may be associated with changes in gray matter<sup>8,9</sup> and white matter structure.<sup>8,10</sup> These uncontrolled human data are consistent with animal imaging data. In nonhuman primates, pathological postmortem cellular changes may explain cortical volume reductions from in vivo imaging data owing to antipsychotic medication.<sup>11-14</sup> These newer data conflict with earlier work demonstrating potential protective effects, particularly of atypical antipsychotics, such as olanzapine.<sup>15</sup>

Uncontrolled human studies are confounded by the fact that patients with the greatest symptom burden often require the highest antipsychotic doses, experience the greatest brain volume changes, and are more likely to misuse substances that can affect brain structure.<sup>16,17</sup> A placebo-controlled trial can more definitively answer the question of the effects of antipsychotic medications on brain structure. To our knowledge, no such study has yet been published.

We conducted a neuroimaging study in the context of a multicenter double-blind randomized placebo-controlled clinical trial (NCT01427608) in patients with psychotic depression, comparing olanzapine plus sertraline with placebo plus sertraline. All patients who entered the neuroimaging study had remission of psychosis and remission or near-remission of depression and were first scanned at the time of randomization, and again 36 weeks following randomization, or at the time of relapse or discontinuation for other reasons (0-36 weeks following randomization).

The primary objective of the imaging study was to compare the effects of olanzapine vs placebo on gray matter structure (cortical and subcortical). We hypothesized that patients in the olanzapine group would demonstrate cortical thinning throughout all lobes but would demonstrate little or no change in surface area or subcortical volume, with the exception of striatal volume increase (given prior work showing effects of antipsychotics on striatal volume<sup>18</sup>). The secondary objec-

## Key Points

**Question** Using a double-blind, randomized, placebo-controlled design, what is the association of olanzapine vs placebo with change in brain structure in humans?

**Findings** In this prespecified secondary analysis imaging study embedded in a clinical trial in people with remitted psychotic depression, olanzapine exposure vs placebo was associated with decline in cortical thickness. However, illness relapse while receiving placebo was potentially associated with a decline in cortical thickness.

**Meaning** Our findings could support a reconsideration of the risks and benefits of antipsychotics and support differential effects on brain structure in those who stay well receiving placebo vs those who relapse.

tive of the study was to compare the effects of olanzapine vs placebo on white matter microstructure. We hypothesized that patients in the olanzapine group would experience decrease in fractional anisotropy and increase in mean diffusivity of white matter compared with those in the placebo group. Our exploratory objective was to assess effects of active illness (ie, relapse) on brain structure.

## Methods

### Design

The study was conducted at 5 academic centers: the University of Massachusetts Medical School; the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; the University of Toronto (the Centre for Addiction and Mental Health and the University Health Network), Toronto, Ontario, Canada; and the Weill Medical College of Cornell University, New York, New York (scanning occurred at the Nathan Kline Institute for Psychiatric Research). The study was approved by the institutional review board/research ethics board at each site. Following written consent to the clinical trial protocol (Study of the Pharmacotherapy of Psychotic Depression II [STOP-PD II]),<sup>19</sup> participants were offered participation in the neuroimaging study. The STOP-PD II was divided into 3 consecutive phases: first, up to 12 weeks of short-term open-label treatment with with sertraline (target dose: 150-200 mg/d) and olanzapine (target dose: 15-20 mg/d) to attain remission; second, an 8-week stabilization phase to ensure that remission is sustained; and third, a 36-week randomized clinical trial (RCT) comparing the efficacy of sertraline plus olanzapine and sertraline plus placebo in preventing relapse of psychotic depression.<sup>20</sup> The RCT showed that people with remitted psychotic depression receiving sertraline olanzapine were less likely to relapse than those receiving sertraline plus placebo. Magnetic resonance imaging (MRI) scanning occurred at the time of randomization, and again either at the end of the 36-week RCT or at the time of relapse (or discontinuation). Study investigators and staff of the neuroimaging study were blind to the randomization throughout. The formal trial protocols can be found in [Supplement 1](#).

## Participants

The STOP-PD II participants were aged 18 to 85 years and met diagnostic criteria for nonbipolar major depressive disorder with psychotic features based on the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders administered by a trained research associate. As previously described,<sup>19</sup> the study's exclusion criteria included current or lifetime *DSM-IV-TR* criteria for any other psychotic disorder, bipolar disorder, or intellectual disability; *DSM-IV-TR* criteria for body dysmorphic disorder or obsessive-compulsive disorder; *DSM-IV-TR*-defined dementia preceding the index episode of depression or a 26-item Informant Questionnaire on Cognitive Decline in the Elderly<sup>21</sup> mean score of at least 4 at acute-phase baseline; *DSM-IV-TR*-defined substance abuse or dependence within the preceding 3 months; type 1 diabetes mellitus; neurologic disease that might affect neuromuscular function; and unstable physical illness, although many of the study participants had stable chronic physical problems.

At the end of the stabilization phase, to be eligible for randomization into the RCT (and thus for the neuroimaging study), participants had to be in remission (defined as the resolution of psychotic symptoms and no or minimal depressive symptoms) or near remission (defined as the resolution of psychotic symptoms and a marked decrease in depressive symptoms) and have a Mini-Mental State Examination<sup>22</sup> score of at least 24.<sup>19</sup> Participants with standard contraindications for MRI (eg, metal implants) or an acute/unstable nonmental illness were not eligible for the neuroimaging study.

## Scanning and Analysis of MRI Data

All participants who completed two 3-T MRI scans on the same scanner using the same acquisition parameters were included in the final analyses. Scanner models varied by site; however, prior to study start, efforts were made to harmonize acquisition protocols on key parameters (eTables 1 and 2 in Supplement 2). Gray matter structure (cortical thickness, surface area, and subcortical volumes) was assessed from the high-resolution T1-weighted data. In the cortex, volume is the product of cortical thickness and surface area. We selected, a priori, cortical thickness as our primary outcome measure. Most studies to date have examined antipsychotic effects on volume. However, cortical thickness and surface area are under different genetic, cellular, and environmental control (cortical thickness is under less genetic and more environmental control in relation to surface area and thus may be more susceptible to change).<sup>23</sup> Similarly, most imaging studies of antipsychotics have examined white matter volume. Diffusion tensor imaging (DTI) is an MRI technique that allows for inference of white matter microstructure (ie, organization and integrity of axonal membranes and myelin) based on water molecule diffusion and directionality.<sup>24</sup> Here, we calculated fractional anisotropy (FA) and mean diffusivity (MD), with FA as our a priori secondary outcome measure.

Following processing and quality control of T1-weighted data, mean hemispheric cortical thickness, surface area, and subcortical volumes were obtained using FreeSurfer, version 6.0 longitudinal (Martinos Center for Biomedical Imaging), a within-participant template estimation for unbiased longitudinal

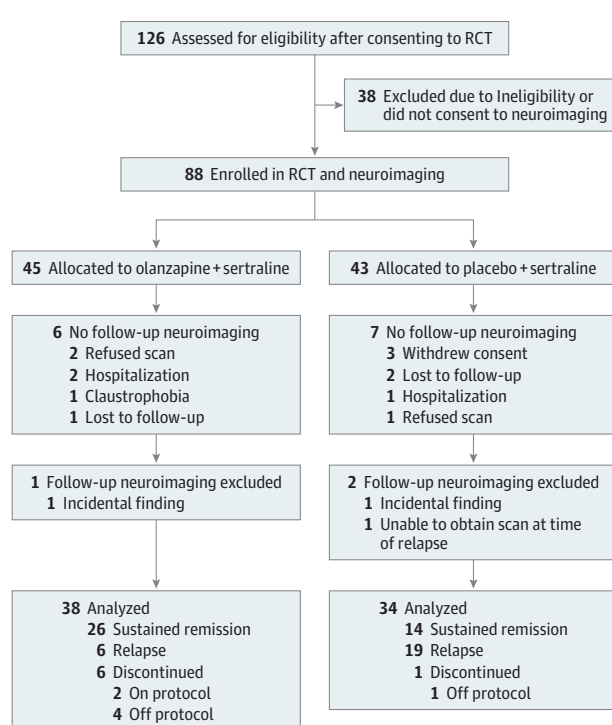
analysis.<sup>25</sup> Cortical regions were then segmented for post hoc analyses of regions of interest (ROIs) using the Desikan-Killiany atlas. Segmentation quality for each participant was visually inspected using ENIGMA protocol guidelines (<http://enigma.ini.usc.edu/protocols/imaging-protocols>).<sup>26</sup> For DTI data, following eddy current correction and tensor fitting, white matter microstructure (indexed as fractional anisotropy and mean diffusivity) was then measured from the DTI skeleton and quality inspected following the ENIGMA-DTI protocol<sup>27</sup> (<http://enigma.ini.usc.edu/ongoing/dti-working-group/>). Mean FA and MD from the white matter skeleton were extracted. Fractional anisotropy and MD were also extracted from 25 white matter ROIs (using the ENIGMA template ROIs of the Johns Hopkins University white matter atlas<sup>28</sup>) for post hoc analyses.

## Statistical Analysis

Mixed-model regression was used (lme4 package in R [the R Foundation]) in the primary and secondary analyses. The primary analysis associated with change in gray matter structure (cortical thickness, surface area, subcortical volumes of thalamus, striatum, and hippocampus) and the secondary analysis change in white matter structure (FA and MD). Time was measured (interval between scans, in days), and a treatment-group by time interaction was modeled, with sex and age as covariates. A fixed intercept was included, along with a random intercept to account for within-participant variability and one to account for site variability. Scan site is included in the error term rather than as a covariate, because as a covariate it would be modeled to an arbitrary reference site. Treatment group is a binary categorical variable (olanzapine or placebo arm). For subcortical volume analysis, total brain volume was also included as a covariate in the model. A sensitivity analysis was also conducted excluding the 5 participants who were scanned at the time of discontinuation off protocol, which is the term used for participants who elected to stop 1 or both randomized study medications but continued to attend for research assessments. Participants who discontinued the RCT prematurely but who remained receiving study medication up until their last assessment were considered on protocol. We ran our primary and secondary analyses 2 times. For our primary outcome measure, a Bonferroni-corrected  $P = .0035$  was considered significant in gray matter (7 tests  $\times$  2 runs: left and right cortical thickness, left and right surface area, thalamic, striatal, and hippocampal volumes). For our secondary outcome measure, a Bonferroni-corrected  $P = .0125$  was used in white matter (2 tests  $\times$  2 runs: mean skeleton FA and MD). All  $P$  values were 2-sided. The second run of the analysis was done to fully control for effects of illness and time, ie, only in those who sustained remission, such that all participant scans were approximately 36 weeks apart with change in brain structure as the dependent variable.

In an exploratory analysis, we directly compared brain structure of those who relapsed receiving placebo with those who relapsed receiving olanzapine and also compared those who relapsed receiving placebo with those who sustained remission receiving placebo. We also explored whether the results of the primary and secondary analyses remained similar in older participants (ie, older than 50 years).

Figure 1. CONSORT Chart



This chart provides numbers regarding enrollment, allocation, follow-up, and analysis of participants initially assessed for eligibility for the neuroimaging study after consenting to the clinical trial.

For the treatment by time interactions, we considered modeling nonlinear effects of time. However, this would have created a stronger contributing effect of those who sustained remission.

## Results

### Participants and Randomization

The first participant entered the RCT phase of STOP-PD II study in March 2012; the final participant exited the RCT in June 2017. Eighty-eight of 126 STOP-PD II participants were eligible and consented to the neuroimaging study; of these, all 88 completed a baseline scan; 75 completed either the 36-week (ie, sustained remission) scan, a scan at relapse, or a scan at treatment protocol discontinuation. Following quality control, 72 of these 75 end scans could be used in the analyses (Figure 1). Forty were performed at the 36-week point, and 32 were performed within 36 weeks following the baseline scan. Baseline characteristics of participants in the olanzapine and placebo groups are available in the Table.

### Outcome Measures

#### Primary Analysis

There was a significant treatment-group by time interaction for cortical thickness (left,  $t = 3.3$ ;  $P = .001$ ; right,  $t = 3.6$ ;  $P < .001$ ), but not surface area (Figure 2A and B). No such

interaction was present for hippocampus, striatum, or thalamus after multiple-comparison correction (eFigure 1 in Supplement 2). The sensitivity analysis revealed the same significant interactions (eg, cortical thickness, left,  $t = 3.6$ ;  $P < .001$ ). When the analyses were restricted to those who sustained remission, olanzapine exposure was associated with a significant reduction compared with placebo exposure for cortical thickness across the 36-week period in the left hemisphere ( $\beta$  [SE], 0.04 [0.009];  $t_{34.4} = 4.7$ ;  $P < .001$ ), and the right hemisphere ( $\beta$  [SE], 0.03 [0.009];  $t_{35.1} = 3.6$ ;  $P < .001$ ) (Figure 2C). For surface area, olanzapine exposure was not associated with a significant reduction in the left hemisphere ( $\beta$  [SE], 477.8 [163.9];  $t_{36.0} = 2.0$ ;  $P = .006$ ) or right hemisphere ( $\beta$  [SE], 143.1 [192.4];  $t_{36.0} = 0.7$ ;  $P = .50$ ) (Figure 2D) compared with placebo. No significant change was found with olanzapine vs placebo exposure in subcortical volumes (eFigure 1 in Supplement 2).

#### Secondary Analysis

There was no significant treatment-group by time interaction for white matter FA, but there was for MD ( $t = -2.6$ ;  $P = .01$ ) (Figure 3A and B). The sensitivity analysis revealed the same interaction for MD ( $t = -2.7$ ;  $P = .01$ ). When the analyses were restricted to those who sustained remission, the olanzapine group experienced no decrease in FA ( $\beta$  [SE], 0.002 [0.002];  $t_{36.0} = 0.7$ ;  $P = .50$ ) compared with the placebo group, nor was there any increase in MD ( $\beta$  [SE],  $-2.0 \times 10^{-5}$  [ $1.0 \times 10^{-5}$ ];  $t_{36.0} = -2.3$ ;  $P = .03$ ), compared with the placebo group (Figure 3C and D) given the multiple comparison correction threshold.

### Effects in Older Participants

When the analyses were restricted to those older than 50 years, the main treatment-group by time findings on cortical thickness (eg, left hemisphere  $t = 2.8$ ;  $P = .007$ ) and reductions in the olanzapine vs placebo group (eg, left hemisphere  $\beta$  [SE], 0.039 [0.0072];  $t_{15.5} = 5.449$ ;  $P < .001$ ) in those who sustained remission demonstrated larger effect sizes. In MD of white matter, effects were also more prominent in the older group (treatment-group by time interaction  $t = -3.4$ ;  $P = .002$ ; increase in the olanzapine group vs placebo group [ $\beta$  (SE),  $-4.7 \times 10^{-5}$  ( $1.4 \times 10^{-5}$ );  $t_{18.0} = -3.3$ ;  $P = .004$ ]).

### Exploratory Analysis

Follow-up exploratory analyses restricted to participants who experienced a relapse showed that those receiving placebo had a significant decrease in cortical thickness compared with those receiving olanzapine. Also, among participants receiving placebo, those who experienced a relapse had a significant decrease in cortical thickness compared with those who sustained remission. Finally, those receiving olanzapine who sustained remission had a significant decrease in cortical thickness compared with those who relapsed receiving olanzapine.

### Post Hoc Analysis of Regional Effects

The literature suggests widespread effects (ie, across cortex) of antipsychotic medications on brain structure. Nevertheless, we conducted post hoc analyses (eFigure 2 and eTable 3

Table. Sociodemographic, Clinical, and Metabolic Characteristics of Participants at the Time of Randomization to Sertraline and Olanzapine or Sertraline and Placebo

| Characteristics   | No. Missing | Group, Mean (SD)                   |                                 | Test Statistic    | df | P Value |
|---|-------------|------------------------------------|---------------------------------|-------------------|----|---------|
|   |             | Sertraline and Olanzapine (n = 38) | Sertraline and Placebo (n = 34) |                   |    |         |
| Age, y  | 0           | 54.4 (15.5)                        | 56.1 (15.5)                     | $t = 0.473$       | 70 | .64     |
| Sex, No. (%)  |             |                                    |                                 |                   |    |         |
| Male  | 0           | 17 (44.7)                          | 15 (44.1)                       | $\chi^2 = 0$      | 1  | >.99    |
| Female  |             | 21 (55.3)                          | 19 (55.9)                       |                   |    |         |
| Race, No. (%)   |             |                                    |                                 |                   |    |         |
| White   | 1           | 32 (84.2)                          | 26 (78.8)                       | Fisher exact test | NA | .65     |
| Black   |             | 3 (7.9)                            | 5 (15.2)                        |                   |    |         |
| Other   |             | 3 (7.9)                            | 2 (6.1)                         |                   |    |         |
| Ethnicity, No. (%)  |             |                                    |                                 |                   |    |         |
| Non-Hispanic  | 0           | 34 (89.5)                          | 28 (82.4)                       | Fisher exact test | NA | .50     |
| Hispanic  |             | 4 (10.5)                           | 6 (17.6)                        |                   |    |         |
| Education   | 0           | 14.4 (3.5)                         | 13.2 (3.5)                      | $t = -1.493$      | 70 | .14     |
| Study site, No. (%)   |             |                                    |                                 | $\chi^2 = 1.772$  | 3  | .62     |
| Cornell   | 0           | 6 (15.8)                           | 7 (20.6)                        | NA                | NA | NA      |
| University of Massachusetts   |             | 8 (21.1)                           | 10 (29.4)                       |                   |    |         |
| Pittsburgh  |             | 6 (15.8)                           | 6 (17.6)                        |                   |    |         |
| Toronto   |             | 18 (47.4)                          | 11 (32.4)                       |                   |    |         |
| No. of lifetime depressive episodes, No. (%)                              |             |                                    |                                 | $\chi^2 = 0$      | 1  | >.99    |
| 1   | 0           | 9 (23.7)                           | 9 (26.5)                        | NA                | NA | NA      |
| ≥2  |             | 29 (76.3)                          | 25 (73.5)                       |                   |    |         |
| Duration of current episode of depression, median (IQR), mo               | 2           | 5.5 (4-11)                         | 6.5 (2-15.2)                    | $H = 0.033$       | 1  | .86     |
| Age at onset of first major depressive episode, y                         | 3           | 37.7 (17.1)                        | 37.4 (20.5)                     | $t = -0.067$      | 67 | .95     |
| Lifetime suicide attempt, No. (%)   |             |                                    |                                 | $\chi^2 = 0.133$  | 1  | .72     |
| Yes   | 0           | 13 (34.2)                          | 14 (41.2)                       | NA                | NA | NA      |
| No  |             | 25 (65.8)                          | 20 (58.8)                       |                   |    |         |
| Treatment resistance in current episode, No. (%) <sup>a</sup>             |             |                                    |                                 |                   |    |         |
| No  | 0           | 36 (94.7)                          | 31 (91.2)                       | Fisher exact test | NA | .66     |
| Yes   |             | 2 (5.3)                            | 3 (8.8)                         |                   |    |         |
| Diagnosis of hyperlipidemia, No. (%)                                      |             |                                    |                                 | $\chi^2 = 0$      | 1  | >.99    |
| Yes   | 0           | 15 (39.5)                          | 14 (41.2)                       | Fisher exact test | NA | .66     |
| No  |             | 23 (60.5)                          | 20 (58.8)                       |                   |    |         |
| Diagnosis of hypertension, No. (%)  |             |                                    |                                 |                   |    |         |
| Yes   | 0           | 10 (26.3)                          | 13 (38.2)                       | $\chi^2 = 0.689$  | 1  | .41     |
| No  |             | 28 (73.7)                          | 21 (61.8)                       |                   |    |         |
| Diagnosis of diabetes, No. (%)  |             |                                    |                                 |                   |    |         |
| Yes   | 0           | 7 (18.4)                           | 8 (23.5)                        | $\chi^2 = 0.059$  | 1  | .81     |
| No  |             | 31 (81.6)                          | 26 (76.5)                       |                   |    |         |
| HAM-D 17 total score  | 0           | 5.1 (3.2)                          | 6.4 (4.1)                       | $t = 1.507$       | 70 | .14     |
| SADS <sup>b</sup>   |             |                                    |                                 |                   |    |         |
| Delusion score  | 0           | 1 (0)                              | 1 (0)                           | NA                | NA | NA      |
| Hallucination score   | 0           | 1 (0)                              | 1 (0)                           | NA                | NA | NA      |
| CGI Severity Score, median (IQR)  | 0           | 1.0 (1.0-1.0)                      | 1.0 (1.0-2.0)                   | $H = 0.155$       | 1  | .69     |
| HADS Anxiety Score  | 1           | 5.7 (3.9)                          | 4.8 (4.2)                       | $t = 0.95$        | 69 | .34     |
| CIRS-G total score  | 0           | 3.5 (3.5)                          | 3.8 (3.2)                       | $t = 0.36$        | 70 | .72     |
| MMSE  | 0           | 28.2 (2.1)                         | 27.8 (2.2)                      | $t = -0.83$       | 70 | .41     |
| Barnes Akathisia Rating Scale Global Score, median (IQR)                  | 0           | 0 (0)                              | 0 (0)                           | NA                | NA | NA      |
| AIMS Overall Severity Score (tardive dyskinesia)                          | 0           | 0 (0)                              | 0 (0)                           | NA                | NA | NA      |
| Simpson Angus Scale total score (parkinsonism), median (IQR) <sup>c</sup> | 0           | 0.0 (0.0-2.0)                      | 1.0 (0.0-2.0)                   | $H = 0.824$       | 1  | .36     |
| Weight, kg  | 0           | 81.74 (16.51)                      | 83.71 (19.28)                   | $t = 0.48$        | 70 | .63     |
| Waist circumference, cm   | 1           | 96.52 (11.68)                      | 100.84 (14.99)                  | $t = 1.41$        | 69 | .16     |
| Total cholesterol, mg/dL  | 1           | 210.2 (52.8)                       | 216.7 (49.6)                    | $t = 0.53$        | 69 | .60     |

(continued)



Table. Sociodemographic, Clinical, and Metabolic Characteristics of Participants at the Time of Randomization to Sertraline and Olanzapine or Sertraline and Placebo (continued)

| Characteristics                     | No. Missing    | Group, Mean (SD)                   |                                 | Test Statistic | df   | P Value |
|-------------------------------------|----------------|------------------------------------|---------------------------------|----------------|------|---------|
|                                     |                | Sertraline and Olanzapine (n = 38) | Sertraline and Placebo (n = 34) |                |      |         |
| Cholesterol, mg/dL                  |                |                                    |                                 |                |      |         |
| LDL                                 | 1              | 131.7 (41.1)                       | 135.6 (42.0)                    | $t = 0.39$     | 69   | .69     |
| HDL                                 | 1              | 54.3 (21.5)                        | 55.2 (17.5)                     | $t = 0.19$     | 69   | .85     |
| Triglycerides, median (IQR), mg/dL  | 1              | 140.6 (98.8-201.0)                 | 121.3 (88.2-166.3)              | $H = 0.946$    | 1    | .33     |
| Glucose, median (IQR), mg/dL        | 1              | 90.0 (84.6-97.0)                   | 93.0 (86.1-100.5)               | $H = 0.358$    | 1    | .55     |
| Insulin, median (IQR), uIU/mL       | 1              | 8.5 (4.4-13.0)                     | 7.4 (4.9-13.0)                  | $H = 0$        | 1    | >.99    |
| HbA <sub>1c</sub> , %               | 1              | 5.8 (1.1)                          | 5.9 (0.8)                       | $t = 0.66$     | 69   | .51     |
| Sertraline dosage, mg/d             | 0              | 163.8 (33.7)                       | 163.2 (34.9)                    | $t = 0.07$     | 70   | .94     |
| Olanzapine dosage, mg/d             | 0              | 14.8 (4.5)                         | 14.8 (3.8)                      | $t = 0.02$     | 70   | .98     |
| Cortical thickness, mm              |                |                                    |                                 |                |      |         |
| Left                                | 0              | 2.41 (0.09)                        | 2.41 (0.11)                     | $t = 0.09$     | 63.2 | .93     |
| Right                               | 0              | 2.42 (0.08)                        | 2.40 (0.11)                     | $t = 0.75$     | 61.5 | .46     |
| Surface area, mm <sup>2</sup>       |                |                                    |                                 |                |      |         |
| Left                                | 0              | 83 584.98 (9259.48)                | 81 101.75 (10 210.53)           | $t = 1.08$     | 67.1 | .29     |
| Right                               | 0              | 83 263.46 (9340.81)                | 81 436.34 (10 146.92)           | $t = 0.79$     | 67.4 | .43     |
| Fractional anisotropy skeleton      | 0 <sup>d</sup> | 0.39 (0.03)                        | 0.38 (0.03)                     | $t = 1.54$     | 68.8 | .13     |
| Mean diffusivity skeleton           | 0 <sup>d</sup> | 0.00142 (0.00017)                  | 0.00136 (0.00019)               | $t = 1.40$     | 67.4 | .17     |
| Hippocampal volume, mm <sup>3</sup> | 0              | 7538.32 (871.37)                   | 7390.00 (1099.58)               | $t = 0.63$     | 62.8 | .53     |
| Striatal volume, mm <sup>3</sup>    | 0              | 16 931.60 (1825.84)                | 16 610.18 (2077.11)             | $t = 0.69$     | 66.2 | .49     |
| Thalamic volume, mm <sup>3</sup>    | 0              | 13 326.38 (1834.30)                | 12 989.71 (1916.03)             | $t = 0.76$     | 68.0 | .45     |

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; CGI, Clinical Global Rating Scale; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; DKEFS, Delis-Kaplan Executive Function Scale; HADS, Hospital Anxiety and Depression Scale; HAM-D 17, 17-Item Hamilton Depression Rating Scale; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MMSE, Mini Mental State Examination; NA, not applicable; SADS, Schedule for Affective Disorders and Schizophrenia.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; hemoglobin A<sub>1c</sub> to proportion of total hemoglobin, multiply by 0.01; insulin to picomoles per liter, multiply by 6.945; triglycerides to millimoles per liter, multiply by 0.0113.

<sup>a</sup> Treatment resistance defined as an antidepressant plus antipsychotic combination rating score of 3 or higher on the Antidepressant Treatment

History Form and/or 7 or more treatments of electroconvulsive therapy during the current episode of psychotic depression.<sup>29</sup>

<sup>b</sup> Unable to perform statistical tests because SADS delusion and hallucination items = 1 for all participants.

<sup>c</sup> Total score of the Simpson Angus Scale excluded the head dropping item.

<sup>d</sup> Diffusion imaging data from all 72 participants with high-quality T1-weighted scan 1 and scan 2 were available; however, 71 of 72 participants with analyzable T1-weighted data had analyzable diffusion-weighted data (37 participants treated with sertraline and olanzapine and 34 participants treated with sertraline and placebo). Because these data are part of the secondary outcome measure, this information is not in the CONSORT chart.

in Supplement 2) using 5% false discovery rate correction, which revealed widespread effects of thickness changes across the cortex consistent with the primary analysis (31 of 68 regions survived correction); however, the largest effect sizes were in frontal and temporal cortex. Four white matter tracts survived false discovery rate correction in MD analyses, predominantly frontotemporal connections.

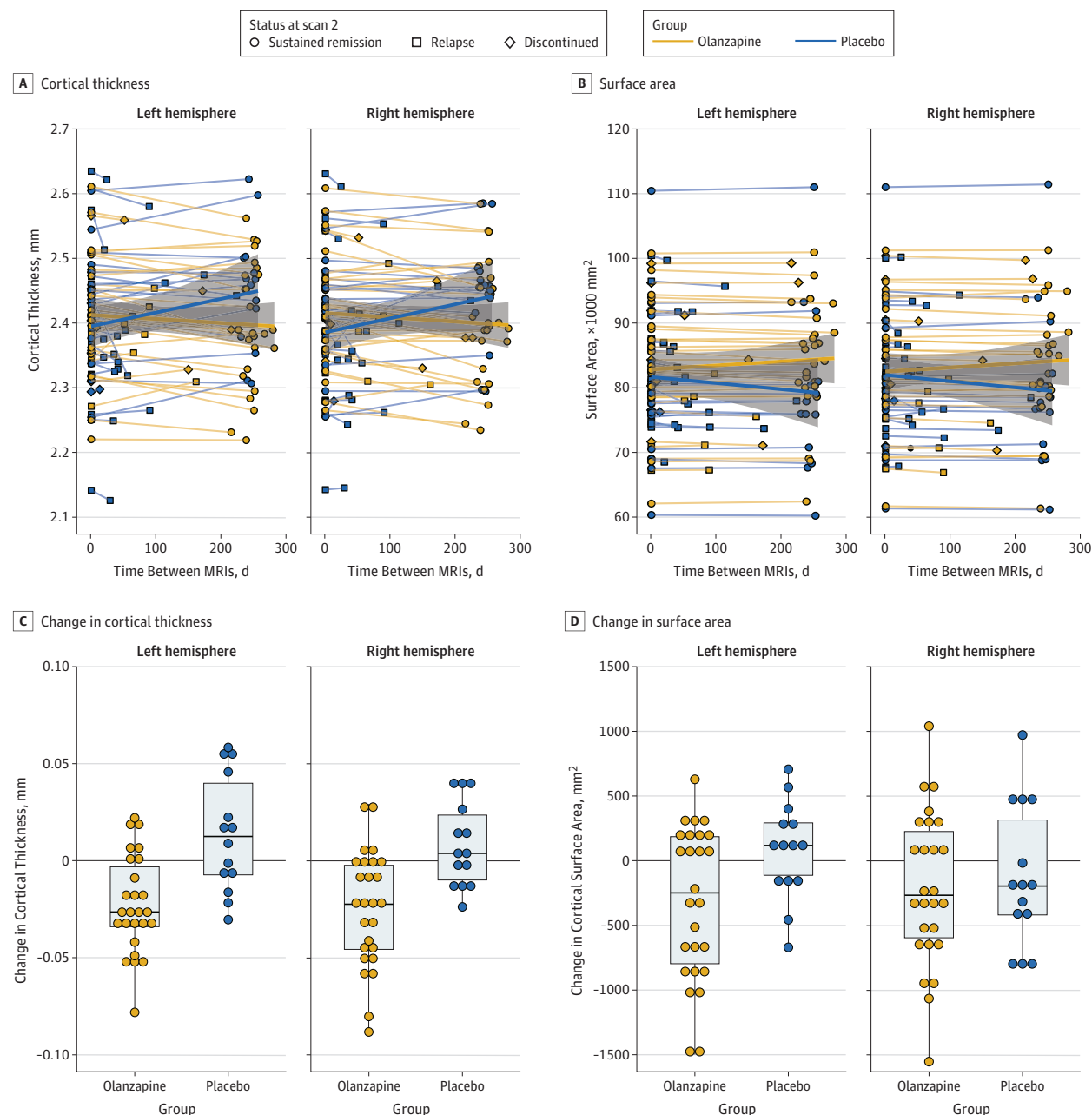
## Discussion

Across all participants who completed both a baseline and follow-up scan with useable neuroimaging data, we found a significant treatment-group  $\times$  time interaction in relation to cortical thickness. This finding suggests differential effects of olanzapine vs placebo on brain structure in those who sustain remission vs those who relapse. When the analyses were restricted to those who sustained remission (without the confound of active illness) we found a significant decrease in cortical thickness compared with placebo across a 36-week period. Olanzapine exposure was not associated with signifi-

cant changes in subcortical volumes. In white matter, there was no effect on FA, but there was an interaction effect with MD. Older participants appeared to be even more susceptible to the effects of medication on brain structure, based on larger effect sizes from the same analyses. Exploratory analyses showed that among those who relapsed, the placebo group experienced a decrease in cortical thickness compared with the olanzapine group; those receiving placebo who relapsed also experienced a decrease in relation to those receiving placebo who sustained remission. When taken together, both olanzapine and illness relapse have an effect on brain structure.

Unlike uncontrolled studies, our randomized double-blind placebo-controlled clinical trial design provides potential evidence for causation: olanzapine administration may cause a decrease in cortical thickness in humans. This randomized study in humans controls for confounders present in previous observational studies such as illness severity or other factors associated with illness that influence brain structure (eg, socioeconomic status, stress, and substance use).<sup>30</sup> We found that the mean reduction in cortical thickness caused by 36 weeks of exposure to olanzapine is equivalent to loss of

Figure 2. Change in Cortical Gray Matter Structure in the Olanzapine and Placebo Groups



Panels A and B demonstrate cortical thickness and surface area at baseline and at the time of the second scan for each participant, which occurred either at remission, relapse, or discontinuation. A significant treatment-group × time interaction for cortical thickness was found, suggesting that there was a different effect of olanzapine vs placebo if a participant sustained remission vs if there was relapse. No such effect was found for surface area. In panels C and D, the data show significant change in cortical thickness but not surface area in

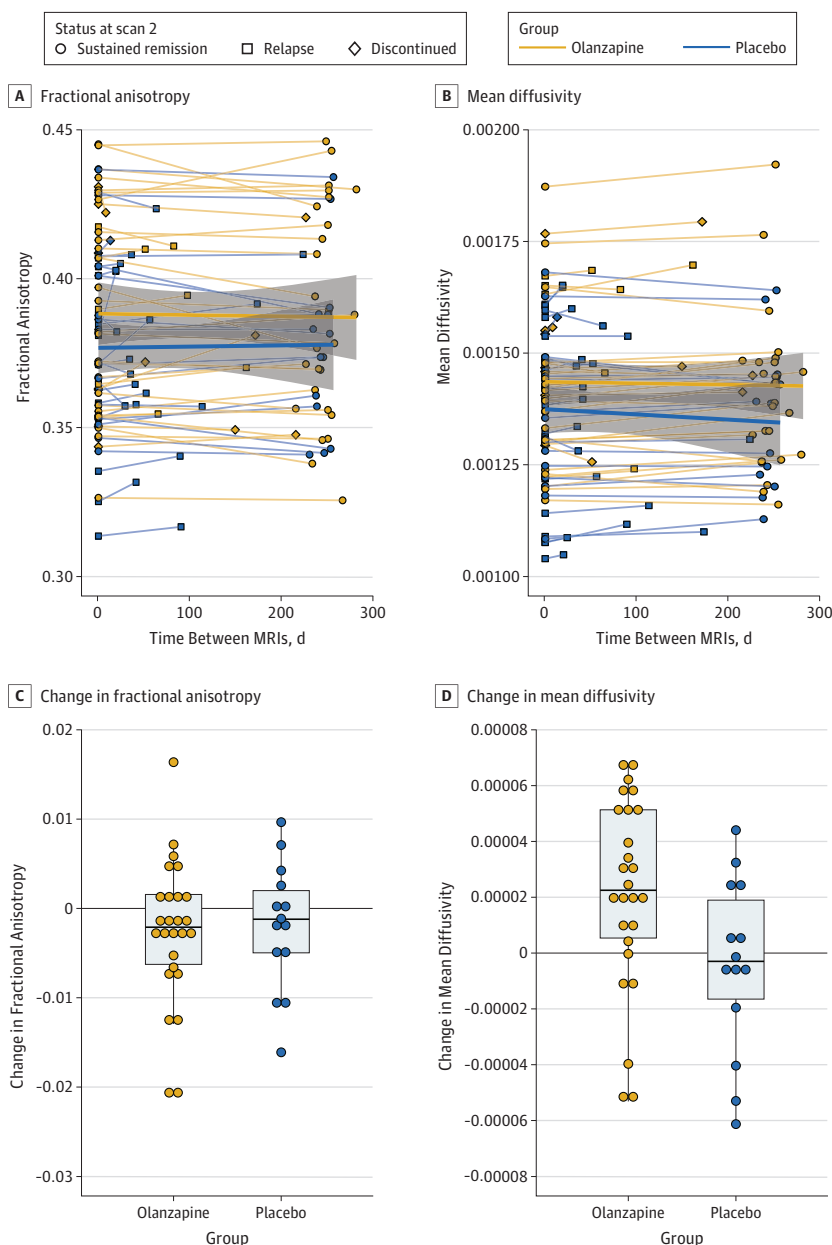
participants who sustained remission. These participants were scanned first at randomization and then again at approximately 36 weeks following their baseline scan. These figures show a significant decrease in cortical thickness (left and right) but not surface area in participants exposed to olanzapine over a 36-week period compared with those receiving placebo. MRI indicates magnetic resonance imaging.

approximately 1.2% of a person's cortex. For context, mean annual change in cortical thickness across the adult life span is 0.35%<sup>31</sup> and 0.59% in normal aging individuals aged 60 to 91 years.<sup>32</sup>

Our findings are consistent with placebo-controlled clinical studies in animals, where long-term exposure was typi-

cally studied over the extrapolated equivalent of several human years. In rodents, long-term exposure to antipsychotic medication causes approximately a 10% decrease in frontal cerebral cortex volume.<sup>12</sup> Similarly, in macaque monkeys, such exposure to antipsychotics causes approximately a 10% decrease in brain volume, again driven by change in cortical

Figure 3. Change in White Matter Microstructure in the Olanzapine and Placebo Groups



Panels A and B demonstrate white matter fractional anisotropy and mean diffusivity at baseline and at the time of the second scan for each participant, respectively, which occurred either at remission, relapse, or discontinuation. A significant treatment-group by time interaction for mean diffusivity was found (but not fractional anisotropy). Panel C demonstrates no change in fractional anisotropy of the white matter skeleton, while panel D compares mean diffusivity in the white matter skeleton in the olanzapine vs placebo group over a 36-week period, which was not significant following multiple comparison correction. MRI indicates magnetic resonance imaging.

structure.<sup>13</sup> Postmortem examination shows that such exposure is associated with decreased cell number, which appears to be caused predominantly by decrease in astrocyte (rather than oligodendrocyte) cell number.<sup>14</sup> Our findings are also consistent with the predominantly cortical effects noted in these animal studies.

Given that reductions in cortical thickness are typically interpreted in psychiatric and neurologic disorders as undesirable, our findings could support a reconsideration of the risks and benefits of antipsychotics. Such reconsideration might make sense when alternatives are present (eg, antidepressants for major depression without psychosis or mood stabilizers for the maintenance treatment of bipolar disorder) or in

off-label use when controlled data do not support their use (eg, for the treatment of anxiety or insomnia). Our data show that such caution may be even more important toward the end of the life span (and we speculate this may also be true early in the life span) when brain change is most dynamic, with heightened vulnerability.<sup>33</sup>

### Limitations

Our findings should be interpreted with some additional considerations. First, we were unable to address any potential effects of sertraline on brain structure given that both groups received this medication. To date, the literature suggests that antidepressants are likely protective for brain structure,<sup>34</sup>



supported by molecular and animal findings<sup>35</sup> as well as indirect evidence owing to association with less cognitive decline in late life.<sup>36</sup> Although scanner models were different across sites, randomization occurred within sites, and the longitudinal design of the scanning and analytical plan meant changes in brain structure were calculated at the individual level within-scanner. Had we used tractography in our diffusion data, we could have examined tract-specific effects of medication and relapse. Finally, while there are definitive cellular changes in rodents and nonhuman primates exposed to antipsychotics, it remains theoretically possible that the MRI changes detected here represent an epiphenomenon<sup>30</sup> rather than actual brain change. Short-term administration of antipsychotics (eg, 24 hours) shows reversible change in cerebral blood flow but less consistent change in brain structure.<sup>37,38</sup> The 36-week (252-day) exposure in this study, coupled with our focus on brain structure, renders the epiphenomenon interpretation unlikely but not impossible. Finally, our data were obtained with 1 specific antipsychotic, olanzapine, and it is possible they do not apply to other antipsychotics. However, based on the wealth of data demonstrating equivalent

efficacy among antipsychotics and similar effects of different antipsychotics on brain structure in both animal and human studies, we speculate that our findings are likely to apply across all medications in this class.

## Conclusions

In psychotic disorders, and when psychosis is present in nonpsychotic disorders, antipsychotics remain an essential treatment. While our data show that antipsychotics may cause adverse changes to brain structure, they also demonstrate that illness relapse may cause similar effects. When psychosis is present, the life-threatening effects of untreated illness<sup>39</sup> outweigh any adverse effects on brain structure in clinical decision-making. Given that nearly half of patients in the STOP-PD II trial sustained remission after being switched from olanzapine to placebo, future studies could provide a predictive model of which patients require long-term treatment with antipsychotics and which patients can safely discontinue them.

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