ORIGINAL ARTICLE

Antipsychotic Drug Effects on Brain Morphology in First-Episode Psychosis

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Background: Pathomorphologic brain changes occurring as early as first-episode schizophrenia have been extensively described. Longitudinal studies have demonstrated that these changes may be progressive and associated with clinical outcome. This raises the possibility that antipsychotics might alter such pathomorphologic progression in early-stage schizophrenia.

Objective: To test a priori hypotheses that olanzapine-treated patients have less change over time in whole brain gray matter volumes and lateral ventricle volumes than haloperidol-treated patients *and* that gray matter and lateral ventricle volume changes are associated with changes in psychopathology and neurocognition.

Design: Longitudinal, randomized, controlled, multisite, double-blind study. Patients treated and followed up for up to 104 weeks. Neurocognitive and magnetic resonance imaging (MRI) assessments performed at weeks 0 (baseline), 12, 24, 52, and 104. Mixed-models analyses with time-dependent covariates evaluated treatment effects on MRI end points and explored relationships between MRI, psychopathologic, and neurocognitive outcomes.

Setting: Fourteen academic medical centers (United States, 11; Canada, 1; Netherlands, 1; England, 1).

Participants: Patients with first-episode psychosis (*DSM-IV*) and healthy volunteers.

Interventions: Random allocation to a conventional antipsychotic, haloperidol (2-20 mg/d), or an atypical antipsychotic, olanzapine (5-20 mg/d).

Main Outcome Measures: Brain volume changes assessed by MRI.

Results: Of 263 randomized patients, 161 had baseline and at least 1 postbaseline MRI evaluation. Haloperidol-treated patients exhibited significant decreases in gray matter volume, whereas olanzapine-treated patients did not. A matched sample of healthy volunteers (n=58) examined contemporaneously showed no change in gray matter volume.

Conclusions: Patients with first-episode psychosis exhibited a significant between-treatment difference in MRI volume changes. Haloperidol was associated with significant reductions in gray matter volume, whereas olanzapine was not. Post hoc analyses suggested that treatment effects on brain volume and psychopathology of schizophrenia may be associated. The differential treatment effects on brain morphology could be due to haloperidol-associated toxicity or greater therapeutic effects of olanzapine.

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Group Information: A list of the members of the HGDH Study Group appears on page 368.

STRUCTURAL BRAIN ABNORmalities have been extensively and consistently described in patients with schizophrenia.[1-3] This pathomorphologic finding has been most commonly demonstrated as brain volume differences involving the ventricular system and cortical and subcortical gray matter regions in patients with schizophrenia compared with matched healthy volunteers. Longitudinal studies using high-resolution magnetic resonance imaging (MRI) to examine brain structure have found that MRI volume (hereafter referred to simply as "volume") changes were progressive over time and related to the illness course and treatment outcome of patients with first-episode,[4-9] chronic,[10,11] and childhood-onset[12,13] schizophrenia. These findings suggest that although schizophrenia may arise from a neurodevelopmental diathesis, its pathophysiology may be progressive after the onset of illness.[14,15] They also raise the question of what role medication may have in mitigating schizophrenia-associated pathomorphologic changes or, alternatively, contributing to such changes. Preclinical studies have suggested the possibility of specific atypical antipsychotic drugs hav-

ing pharmacologic properties that could produce neurotrophic, neurogenetic, or neuroprotective effects.[16-22]

We addressed these questions in a controlled trial of first-episode psychosis, in which patients were randomized to either a conventional antipsychotic (haloperidol) or an atypical antipsychotic (olanzapine). We hypothesized that (1) olanzapine-treated patients would have less change over time in whole brain gray matter (WBGM) volumes and lateral ventricle volumes than haloperidol-treated patients; (2) decreases in gray matter volumes and increases in lateral ventricle volumes over time would be associated with less improvement on measures of psychopathology and neurocognitive functioning; and (3) caudate nuclei volumes would be differentially affected by treatment, increasing in response to haloperidol and with little or no change in response to olanzapine.

METHODS

This longitudinal study was conducted from March 1, 1997, to July 31, 2001, at 14 academic medical centers (11 in the United States, 1 in Canada, 1 in the Netherlands, and 1 in England).

PATIENTS

Patients who presented to clinical services (inpatient, emergency, and outpatient) for evaluation and treatment of psychotic symptoms were enrolled in the study if they met the following inclusion and exclusion criteria: age 16 to 40 years; onset of psychotic symptoms before age 35 years; diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder according to *DSM-IV* criteria (as assessed with the Structured Clinical Interview for *DSM-IV*, Research Version[23]); previous antipsychotic drug treatment of more than 16 cumulative weeks, or treatment with clozapine at any time in the patient's lifetime; no current substance dependence (except caffeine and nicotine) by *DSM-IV* within 1 month before study entry; no current indication of serious suicidal risk; female subjects not pregnant or nursing; premorbid IQ of 70 or more; no requirement of concurrent treatment with anticonvulsants, benzodiazepines (except as allowed for agitation and control of extrapyramidal symptoms), antidepressants, psychostimulants, or other antipsychotic drugs at study entry; and no contraindication for neuroimaging per current regulations from the local regulatory agency (eg, metal prostheses). Each patient (or a patient's authorized legal representative) had to understand the nature of the study and sign an informed consent document. Each site's institutional review board approved the study.

STUDY DESIGN AND PROCEDURES

Patients were randomized to double-blind treatment with olanzapine, 5 to 20 mg/d, or haloperidol, 2 to 20 mg/d, for up to 104 weeks. Permitted concomitant medications included chloral hydrate, 500 to 2000 mg/d; lorazepam, 1 to 8 mg/d; *or* diazepam, 5 to 40 mg/d, for the management of agitation, general behavior disturbances, and/or insomnia. Concomitant medications were allowed only for a cumulative duration of no more than 21 days.

If clinically important extrapyramidal symptoms emerged, anticholinergic medication (benztropine mesylate or biperiden, up to 6 mg/d; propranolol hydrochloride, 10-80 mg/d; or procyclidine hydrochloride [oral or intramuscular administration of 5-10 mg, 2-3 times daily, up to 30 mg/d]) was also permitted. Antidepressants (except fluoxetine hydrochloride) and/or mood stabilizers were not allowed in the first 12 weeks of the study but could be added if clinically indicated thereafter.

EFFICACY ASSESSMENTS

Patients were assessed by MRI at weeks 0 (baseline), 12, 24, 52, and 104. Patients who dropped out were assessed by MRI until the point at which they dropped out. A very small number of subjects (12) missed a scheduled MRI assessment but did not drop out and were assessed at the next scheduled MRI assessment. All MRI studies were performed with a 1.5-T MRI system. Six of the 8 imaging sites used Signa scanners (General Electric Co, Milwaukee, Wis), and 2 sites used a Gyroscan scanner (Philips Medical Systems, Best, the Netherlands). Two imaging centers studied subjects from more than 1 clinical site. Each subject laid supine with his or her head situated in the head holder for the radiofrequency coil. Two image-intensity standards were placed on either side of the subject's head. The imaging protocol included 3-dimensional T1-weighted, inversion recovery–prepared spoiled gradient-recalled acquisition in steady state images ($0.94 \times 0.94 \times 1.50$ mm, axial direction) and contiguous proton density and T2-weighted fast spin-echo images ($0.94 \times 0.94 \times 3.00$ mm, axial slicing direction). Quality-control scans were performed twice a month on each MRI system with standardized imaging phantoms. The imaging component of the study was centrally coordinated (by one of us [C.C.] at Duke Imaging and Analysis Laboratory, Durham, NC) and included site training, MRI system monitoring, and centralized data analysis. The coordinating center remained blinded throughout the trial. Every data set was processed by means of an automated, atlas-based, multichannel brain-tissue segmentation program that generates detailed maps of gray matter, white matter, and cerebrospinal fluid.[24] This processing includes a bias-field correction that adjusts for intensity inhomogeneities in the data sets. On the basis of Talairach coordinates, a 3-dimensional brain atlas was divided into 16 discrete boxes (parcellated volumes) for regional measurements. The image sets were aligned to the atlas before the automated, atlas-based, multichannel segmentation was applied. Volumes of gray and white matter and cerebrospinal fluid were extracted from each of the 16 parcellated volumes. Anatomically guided combinations of these volumes approximate the frontal, temporal, parietal, and occipital lobes. A rater-guided connectivity-based masking method was used to separate the lateral ventricles from voxel-based cerebrospinal fluid segmentation. Caudate volumes were obtained with manual outlining. Rigorous standardization and quality-control procedures were used, and reliability of measurements across sites was established and maintained throughout the study.[25]

Psychopathology and neurocognitive outcomes were the other primary assessments of efficacy. Psychopathology was assessed by the 30-item Positive and Negative Syndrome Scale (PANSS)[26] (1-7 severity score) and Clinical Global Impressions–Severity[27] scale (1-7 score). Neurocognitive function was assessed by a neuropsychological test battery that evaluated attention, verbal fluency, verbal learning and memory, working memory, visuomotor processing, and motor speed. (Complete methods for this clinical trial, including psychopathology and neurocognitive assessments, have been previously described.[28,29])

HEALTHY VOLUNTEERS

Fifty-eight healthy volunteers matched to the patients' demographic characteristics were ascertained from respondents to advertisements at 4 of the 14 study sites (University of North Caro-

lina, Chapel Hill; University of Toronto, Toronto, Ontario; Harvard Medical School, Boston, Mass; and Institute of Psychiatry, Maudsley Hospital, London, England). Volunteers were screened for medical and psychiatric history in face-to-face interviews and underwent a physical examination and laboratory testing to rule out medical or psychiatric conditions.

STATISTICAL METHODS

Two analysis populations were used to analyze the MRI data: the intent-to-treat (ITT) population (all randomized patients who received at least a baseline scan) and a modified ITT (MITT) population (that subset of the ITT population who received the baseline MRI and at least 1 postbaseline MRI during follow-up period under experimental treatment). The primary analysis used this MITT population, since it was only possible to estimate changes in subjects with baseline and at least 1 postbaseline MRI assessment. To ensure that our findings were not an artifact of the MITT population, we repeated the primary analyses including the subjects who received baseline scans only, carrying forward observations for these patients. This was a conservative sensitivity analysis, because carrying forward baseline observations for subjects with no postbaseline measurements created in both treatment groups a cohort of subjects for whom MRI measures did not change over time, thus minimizing the differences between the means over time. The primary analysis of the MITT population is the analysis presented.

All analyses were conducted with SAS 8.2 (SAS Institute Inc, Cary, NC). We used random-coefficient mixed models to compare the 2 treatments regarding changes over time (baseline to weeks 12, 24, 52, and 104) in the volumes of 7 primary MRI regions of interest (ROIs): whole brain, WBGM, whole brain white matter, whole brain fluid, lateral ventricles, third ventricle, and caudate nucleus. A Bonferroni-corrected α of .05/7 = .00714 was used to control for multiple comparisons. This model fitted separate intercepts, linear slopes, and quadratic slopes for the 2 treatments over the 5 time points. We considered covariates such as investigator, treatment × investigator interaction, sex, duration of illness, and intracranial volume. We eliminated sex as a covariate because sex-specific volume differences could be explained by intracranial volume if necessary. We used WBGM as the response variable for which we refined the model and eliminated covariates, one by one, since they either were nonsignificant or did not appreciably alter the treatment effects, and the resulting final model contained as predictors only drug treatment (olanzapine or haloperidol) and duration of illness. Having arrived at the set of predictors, we fit the same simple and straightforward model to the 7 primary ROIs, as we believed it would be inappropriate to select potentially different individual sets of covariates for each ROI. From the full model, we eliminated all covariates except duration of illness, one by one, since each either was not significantly related to response or did not appreciably alter the treatment effects. The final random-coefficient, mixed-growth-curve model used baseline-to-observation point as the response variable (with separate intercepts, linear slopes, and quadratic slopes for each therapy), using duration of illness as a covariate. The same model was fit to the secondary ROIs (frontal, temporal, parietal, and occipital gray matter volumes). As a secondary analysis to place these effects in context, we obtained volumes on healthy controls on 3 occasions (baseline, week 12, and week 52) and did a similar mixed-model analysis, although the duration-of-illness covariate was omitted because the controls were healthy.

To examine the associations between the changes in morphologic variables, psychopathology variables, and neurocognitive functioning in response to treatment, we used repeated-measure mixed-model analysis with observed cases at each time point. (All variables were selected from a priori hypotheses including MRI variables [WBGM, lateral ventricular], psychopathology variables [PANSS total, positive, and negative subscales], and the first principal component derived from the cognitive battery.) Changes in PANSS scores at follow-ups were modeled as repeated measures, whereas the concurrent MRI changes and interaction between therapy and MRI changes were modeled as time-dependent covariates. Other non–time-dependent covariates included baseline PANSS score, age, sex, investigator, and therapy. The same modeling approach was applied to the neurocognitive variable.

Demographic information and baseline volumes were presented as descriptive statistics. Categorical data were evaluated by Fisher exact and χ^2 tests. All hypothesis tests were performed with a 2-sided $\alpha = .05$.

For this study, the protocol-designated primary analysis consisted of comparisons between haloperidol and olanzapine on changes from baseline for the 7 primary ROIs. All other analyses were designated as secondary or exploratory, and findings resulting from those analyses should be considered to be suggestive of hypotheses for future studies.

RESULTS

Figure 1 presents the patient flowchart. Of the 263 patients randomized (ITT), 239 had baseline MRI, and 161 (MITT) received a baseline and at least 1 follow-up MRI measure. The demographic and clinical characteristics of the MITT sample are given in **Table 1**. The ITT and MITT samples did not differ significantly with respect to demographic and clinical characteristics. Among the MITT patients, the treatment groups differed significantly on duration of illness; this difference was used as a covariate in further MRI analyses.

TREATMENT RESPONSE: MRI

Table 2 and **Table 3** contain results for the ROI-specific volume changes (by treatment group) from baseline to each time point. The final model for all ROIs was based on effect, covariate, and covariance structure selection used with WBGM.

Using a .00714 significance level, corrected analyses of the primary ROIs demonstrated a significant difference in WBGM volume change between the 2 treatment groups at weeks 12 and 24 (Table 2). **Figure 2** shows the WBGM mean changes for weeks 12, 24, 52, and 104. The olanzapine group appeared to largely retain WBGM, whereas the haloperidol group appeared to lose gray matter over time. Most of the decline in the haloperidol group appeared to occur during the first 12 weeks. Although the magnitude of the differences between the groups remained reasonably constant over time, significance was lost at the later time points because the standard error of the estimates increased as a result of increasing patient dropouts. Although no consistent treatment effects met the multiplicity-corrected $\alpha = .00714$ for the other ROIs, increases in lateral ventricle and caudate nucleus volumes reached uncorrected significance levels of .05 at weeks 24, 52, and 104 (Table 2). To understand whether the gray matter was changing differentially, we examined frontal, temporal, parietal, and occipital gray matter changes (Table 3). For frontal gray matter, a significant

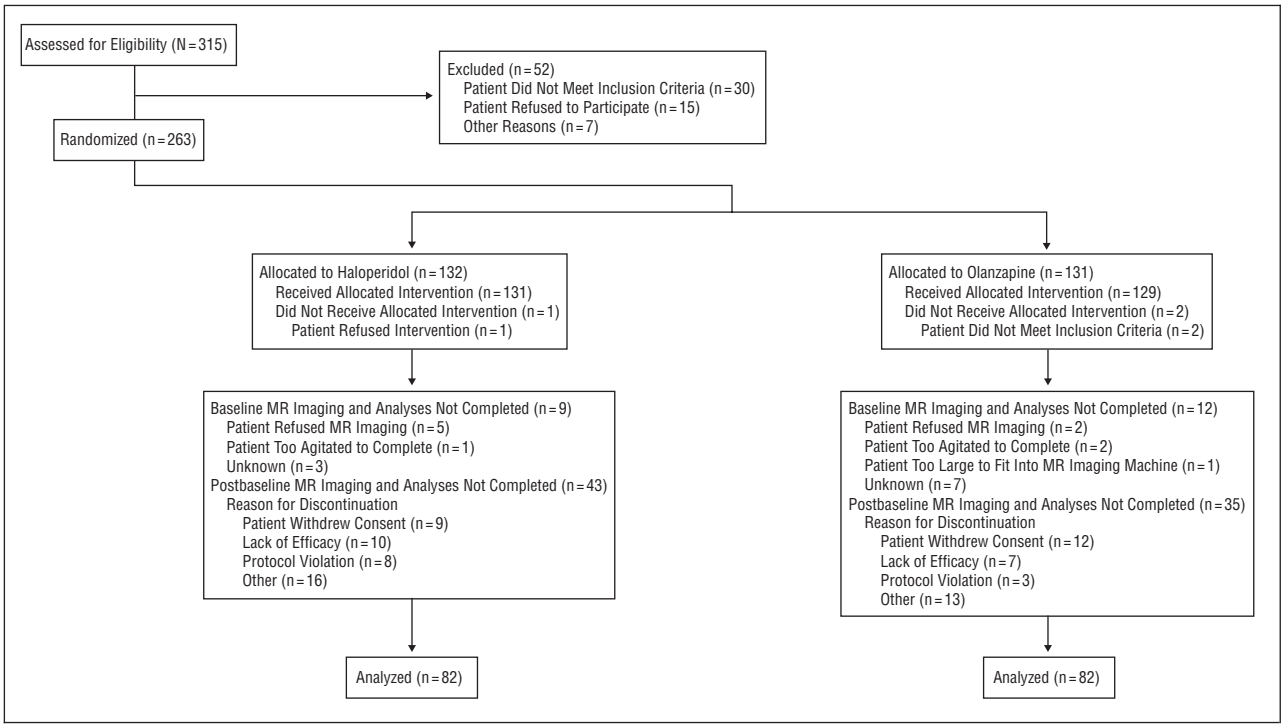

Figure 1. Flowchart of patient sample ascertained and assessed. MR indicates magnetic resonance.

Table 1. Demographic and Clinical Characteristics of 161 Patients (MITT Sample) and 62 Normal Controls

Variable	All Patients (N = 161)	Olanzapine (n = 82)	Haloperidol (n = 79)	Controls (n = 62)	*P* Value: Hal vs Olz	*P* Value: Patients vs Controls
Age, mean (SD, y)	23.85 (4.56)	23.60 (4.50)	24.11 (4.64)	25.53 (4.13)	.51*	.005*
Duration of previous antipsychotic use, d						
Mean (SD)	40.73 (71.55)	40.00 (37.67)	41.58 (97.76)	NA	.15*†	NA
Median (minimum, maximum)	23.00 (1.00, 705.00)	26.50 (1.00, 144.00)	20.00 (1.00, 705.00)	NA		
Duration of illness, wk						
Mean (SD)	65.51 (57.33)	54.11 (50.70)	77.33 (61.60)	NA	.007*	NA
Median (minimum, maximum)	45.29 (3.14, 248.70)	35.29 (3.14, 210.00)	58.43 (4.57, 248.70)	NA		
Sex, No. (%)						
Male	136 (84.5)	65 (79.3)	71 (89.9)	40 (64.5)	.08	.002
Female	25 (15.5)	17 (20.7)	8 (10.1)	22 (35.5)		
Race, No. (%)						
White	78 (48.5)	40 (48.8)	38 (48.1)	38 (61.3)	.91‡	.17‡
African descent	64 (39.8)	31 (37.8)	33 (41.8)	17 (27.4)		
East Asian	5 (3.1)	2 (2.4)	3 (3.8)	5 (8.1)		
West Asian	2 (1.2)	1 (1.2)	1 (1.3)	0 (0.0)		
Hispanic	8 (5.0)	5 (6.1)	3 (3.8)	1 (1.6)		
Other	4 (2.5)	3 (3.7)	1 (1.3)	1 (1.6)		
Diagnosis, No. (%)						
Schizophrenia	104 (64.6)	46 (56.1)	58 (73.4)	NA	.08‡	NA
Schizophreniform disorder	43 (26.7)	27 (32.9)	16 (20.3)	NA		
Schizoaffective disorder	14 (8.7)	9 (11.0)	5 (6.3)	NA		
Previous antipsychotic use, No. (%)						
Yes	116 (72.1)	63 (76.8)	53 (67.1)	NA	.22‡	NA
No	45 (28.0)	19 (23.2)	26 (32.9)	NA		

Abbreviations: Hal, haloperidol; MITT, modified intent-to-treat; NA, not applicable; Olz, olanzapine.
*Two-sided Wilcoxon rank sum test using normal approximation and continuity correction.
†Calculated only for patients with any previous antipsychotic use (n = 115 [olanzapine, 62; haloperidol, 53]).
‡Fisher exact test.

Table 2. Changes in MRI Volumes for Primary Regions of Interest by Treatment Group (Baseline to Weeks 12, 24, 52, and 104)

				Observed Case Mean Changes From Baseline and Mixed-Model *P* Values						
		Baseline		Week 12				Week 24		
ROI	Therapy	N	Mean (SE), cm³	N	Mean (SE), cm³	*P* Value*	*P* Value†	N	Mean (SE), cm³	*P* Value*
WB	Olz	82	1155.01 (14.38)	73	4.74 (2.82)	.10	.66	65	2.30 (2.64)	.05
	Hal	79	1155.76 (13.16)	69	−3.26 (2.93)		.28	47	−6.22 (3.58)	
	Con	52	1181.93 (17.16)	52	1.74 (3.30)					
WBGM	Olz	82	683.99 (8.78)	73	2.65 (1.97)	.002	.93	65	−0.88 (2.05)	.002
	Hal	79	685.79 (8.23)	69	−5.85 (1.92)		.005	47	−10.36 (2.48)	
	Con	52	699.24 (10.29)	52	2.01 (2.28)					
WBWM	Olz	82	471.01 (5.98)	73	2.08 (1.88)	.39	.55	65	3.18 (2.22)	.63
	Hal	79	469.97 (5.38)	69	2.59 (2.23)		.17	47	4.13 (2.69)	
	Con	52	482.69 (7.33)	52	−0.28 (2.13)					
WBF	Olz	82	226.07 (4.05)	73	2.77 (1.55)	.14	.63	65	6.89 (1.42)	.56
	Hal	79	230.75 (3.87)	69	6.67 (1.80)		.18	47	5.70 (2.45)	
	Con	52	231.33 (4.78)	52	2.80 (2.51)					
LV	Olz	80	20.74 (0.97)	71	−0.05 (0.33)	.08	.86	64	−0.31 (0.36)	.27
	Hal	77	20.78 (1.29)	68	0.68 (0.33)		.01	46	0.62 (0.55)	
	Con	52	20.46 (1.18)	52	−0.28 (0.23)					
CN	Olz	80	8.89 (0.19)	71	−0.36 (0.13)	.12	.18	64	−0.23 (0.15)	.03
	Hal	77	8.62 (0.15)	68	0.03 (0.13)		.92	46	−0.04 (0.14)	
	Con	52	9.09 (0.16)	52	−0.01 (0.15)					
TV	Olz	80	8.89 (0.19)	71	−0.01 (0.03)	.71	.36	64	−0.11 (0.04)	.39
	Hal	77	8.62 (0.15)	68	−0.01 (0.03)		.87	46	−0.11 (0.05)	
	Con	52	9.09 (0.16)	52	−0.02 (0.03)					

		Observed Case Mean Changes From Baseline and Mixed-Model *P* Values						
		Week 52				Week 104		
ROI	Therapy	N	Mean (SE), cm³	*P* Value*	*P* Value†	N	Mean (SE), cm³	*P* Value*
WB	Olz	43	3.18 (2.73)	.16	.34	24	10.26 (4.04)	.78
	Hal	32	−9.81 (4.16)		.03	10	−3.32 (12.18)	
	Con	44	7.10 (5.41)					
WBGM	Olz	43	−3.70 (1.72)	.049	.03	24	0.91 (3.90)	.16
	Hal	32	−11.69 (3.41)		<.001	10	−12.80 (11.89)	
	Con	44	4.12 (3.64)					
WBWM	Olz	43	6.88 (2.93)	.90	.33	24	9.36 (3.23)	.31
	Hal	32	1.87 (2.85)		.43	10	9.48 (7.17)	
	Con	44	2.98 (2.80)					
WBF	Olz	43	3.28 (1.82)	.52	.07	24	7.75 (2.25)	.84
	Hal	32	5.25 (3.20)		.18	10	6.47 (3.86)	
	Con	44	−0.10 (3.43)					
LV	Olz	42	0.37 (0.55)	.66	.99	25	2.28 (0.84)	.10
	Hal	31	0.37 (0.57)		.80	10	0.68 (1.57)	
	Con	44	0.34 (0.26)					
CN	Olz	42	−0.52 (0.16)	.02	.003	25	−0.30 (0.28)	.04
	Hal	31	0.12 (0.18)		.58	10	0.39 (0.37)	
	Con	44	0.17 (0.13)					
TV	Olz	42	−0.01 (0.06)	.06	.26	25	0.14 (0.09)	.23
	Hal	31	−0.11 (0.07)		.40	10	0.01 (0.13)	
	Con	44	−0.12 (0.02)					

Abbreviations: CN, caudate nucleus; Con, control; Hal, haloperidol; LV, lateral ventricle; MRI, magnetic resonance imaging; Olz, olanzapine; ROIs, regions of interest; TV, third ventricle; WB, whole brain; WBF, whole brain fluid; WBGM, whole brain gray matter; WBWM, whole brain white matter.

**P* values are from an F test at each time point, comparing olanzapine- and haloperidol-treated patients with respect to mean change for each ROI from baseline, within the context of a mixed model. Each model contained a random intercept and therapy, therapy by week, therapy by week squared, and duration of illness fixed effects. Each model was fit assuming a compound symmetric covariance structure with different variance components for each therapy.

†*P* values are from an F test at each time point, comparing olanzapine-treated and control patients or haloperidol-treated and control patients with respect to mean change for each ROI from baseline, within the context of a mixed model. Each model contained a random intercept fixed effects for therapy and the therapy × week interaction. The model was fit assuming a compound symmetric covariance structure with different variance components for each of the 3 therapy groups.

difference occurred between the therapies at weeks 12 and 24 (using the same multiplicity-corrected $\alpha = .00714$). When not correcting for multiple comparisons ($\alpha = .05$), significant differences were seen for temporal gray matter (weeks 24 and 52) and parietal gray matter (weeks 12 and 24).

Table 3. Changes in MRI Volumes for Secondary Regions of Interest by Treatment Group (Baseline to Weeks 12, 24, 52, and 104)

				Observed Case Mean Changes From Baseline and Mixed-Model *P* Values						
		Baseline		Week 12				Week 24		
ROI	Therapy	N	Mean (SE), cm³	N	Mean (SE), cm³	*P* Value*	*P* Value†	N	Mean (SE), cm³	*P* Value*
FGM	Olz	82	310.65 (3.99)	73	0.68 (1.14)	<.001	.34	65	−1.02 (1.31)	.003
	Hal	79	312.24 (3.82)	69	−4.59 (1.04)		<.001	47	−6.80 (1.36)	
	Con	52	317.73 (4.75)	52	2.22 (1.16)					
TGM	Olz	82	133.54 (1.69)	73	1.24 (0.55)	.19	.33	65	1.06 (0.58)	.03
	Hal	79	133.55 (1.75)	69	0.19 (0.51)		.75	47	−0.40 (0.70)	
	Con	52	136.36 (2.30)	52	0.40 (0.82)					
PGM	Olz	82	122.86 (1.84)	73	0.75 (0.52)	.02	.20	65	−0.05 (0.55)	.03
	Hal	79	122.73 (1.71)	69	−0.94 (0.51)		.28	47	−1.97 (0.65)	
	Con	52	126.39 (1.99)	52	−0.36 (0.58)					
OGM	Olz	82	116.93 (1.65)	73	−0.01 (0.41)	.78	.94	65	−0.87 (0.43)	.55
	Hal	79	117.25 (1.43)	69	−0.51 (0.46)		.84	47	−1.18 (0.54)	
	Con	52	118.74 (1.85)	52	−0.24 (0.55)					

		Observed Case Mean Changes From Baseline and Mixed-Model *P* Values						
		Week 52				Week 104		
ROI	Therapy	N	Mean (SE), cm³	*P* Value*	*P* Value†	N	Mean (SE), cm³	*P* Value*
FGM	Olz	43	−3.16 (1.21)	.15	.03	24	−0.08 (2.57)	.15
	Hal	32	−7.56 (2.04)		<.001	10	−7.32 (6.10)	
	Con	44	0.54 (1.78)					
TGM	Olz	43	1.81 (0.60)	.02	.86	24	1.47 (0.90)	.23
	Hal	32	−0.92 (0.91)		.03	10	−1.33 (2.56)	
	Con	44	1.89 (1.08)					
PGM	Olz	43	−0.86 (0.60)	.14	.05	24	0.53 (1.17)	.05
	Hal	32	−1.71 (0.74)		.002	10	−3.65 (2.09)	
	Con	44	0.70 (0.71)					
OGM	Olz	43	−1.49 (0.68)	.72	.009	24	−1.02 (0.88)	.34
	Hal	32	−1.50 (0.71)		.007	10	−0.49 (2.47)	
	Con	44	0.99 (0.79)					

Abbreviations: See Table 2; FGM, frontal gray matter; OGM, occipital gray matter; PGM, parietal gray matter; TGM, temporal gray matter.

**P* values are from an F test at each time point, comparing olanzapine- and haloperidol-treated patients with respect to mean change for each ROI from baseline, within the context of a mixed model. Each model contained a random intercept and therapy, therapy by week, therapy by week squared, and duration of illness fixed effects. Each model was fit assuming a compound symmetric covariance structure with different variance components for each therapy.

†*P* values are from an F test at each time point, comparing olanzapine-treated and control patients or haloperidol-treated and control patients with respect to mean change for each ROI from baseline, within the context of a mixed model. Each model contained a random intercept and fixed effects for therapy and the therapy × week interaction. The model was fit assuming a compound symmetric covariance structure with different variance components for each of the 3 therapy groups.

Caudate nucleus volumes increased in the haloperidol-treated patients compared with the olanzapine group, the differences reaching significance ($\alpha = .05$) at weeks 24, 52, and 104 (Table 2).

PATIENTS AND HEALTHY VOLUNTEERS: MRI

A random-coefficient mixed model was fit for data from both the patient groups and the control group. Figure 2 displays WBGM volume changes from baseline to weeks 12 and 52 for patients and controls. Using the same multiplicity-corrected $\alpha = .00714$, haloperidol-treated patients exhibited significant decreases in WBGM compared with controls at weeks 12 ($P = .005$) and 52 ($P < .001$), whereas olanzapine-treated patients did not. Using $\alpha = .05$, we secondarily examined gray volume in individual lobes and found significant differences for frontal gray between the haloperidol and control groups at weeks 12 ($P < .001$) and 52 ($P < .001$). A similar pattern of significant differences in temporal and parietal gray matter volumes was seen at week 52 ($P = .03$ and $P = .002$, respectively).

SENSITIVITY ANALYSES

Data from 239 patients with baseline, but no follow-up, MRIs were used for these analyses. (At all time points in both the ITT and MITT samples, more haloperidol-treated patients than olanzapine-treated patients dropped out.) By week 104, 29 olanzapine-treated patients and 14 haloperidol-treated patients remained in the MITT sample ($P = .01$; Fisher exact test). (Since the proportion of patients who dropped out was larger in the haloperidol group than in the olanzapine group, this greater number of baseline observations carried forward would have resulted in a smaller change in the haloperidol group. In fact, the opposite happened: there was still little or no change in the olanzapine group, with change in the halo-

peridol group.) The results of this analysis were similar to those of the primary MITT analysis. In this secondary analysis, the groups differed significantly, with haloperidol-treated patients showing greater reductions than olanzapine-treated patients in WBGM at weeks 12 (mean [SE]: –3.42 cm^3 [1.18 cm^3] vs 1.24 cm^3 [1.17 cm^3]; $P=.008$), 24 (–4.26 cm^3 [1.11 cm^3] vs –0.04 cm^3 [1.17 cm^3]; $P=.01$), 52 (–5.41 cm^3 [1.20 cm^3] vs –1.75 cm^3 [1.30 cm^3]; $P=.004$), and 104 (–4.47 cm^3 [1.23 cm^3] vs –0.25 cm^3 [1.34 cm^3]; $P=.01$); and in frontal gray matter specifically at weeks 12 (–2.89 cm^3 [0.70 cm^3] vs 0.17 cm^3 [0.77 cm^3]; $P=.004$), 24 (–3.20 cm^3 [0.66 cm^3] vs –0.76 cm^3 [0.71 cm^3]; $P=.01$), and 104 (–3.24 cm^3 [0.73 cm^3] vs –1.06 cm^3 [0.81 cm^3]; $P=.047$). Other sensitivity analysis results were also consistent with the results found in the MITT sample.

BRAIN MORPHOLOGY AND CLINICAL RESPONSE

There were significant associations between changes in PANSS scores and lateral ventricular volumes (PANSS total: $F_{1,207}=4.76$, $P=.03$; PANSS negative: $F_{1,208}=7.74$, $P=.006$). Greater improvements in PANSS total and negative scores were associated with less lateral ventricular volume increase for the olanzapine group. For olanzapine-treated patients, each 1-cm^3 increase in lateral ventricular volume was associated with 0.8-point reduction in improvement on PANSS total subscale (SE=0.3, $F_{1,207}=5.86$, $P=.01$, effect size g=0.36, small to moderate association) and 0.3-point reduction in improvement on PANSS negative (SE=0.1, $F_{1,208}=7.02$, $P=.01$, g=0.37, small to moderate association). Similar associations were not significant for the haloperidol group. We also found group differences in associations between changes in neurocognitive functioning and changes in gray matter volumes (WBGM: $F_{1,133}=2.69$, $P=.10$; parietal gray: $F_{1,133}=5.24$, $P=.02$; frontal gray: $F_{1,133}=5.71$, $P=.02$). For haloperidol-treated patients, less improvement in neurocognitive functioning was associated with greater decrease in gray matter volumes. This association was moderate ($F_{1,133}=6.92$, $P=.01$, g=0.46) for the WBGM volume and greatest for the frontal and parietal lobes ($F_{1,133}=11.56$, $P=.001$, g=0.59 and $F_{1,133}=9.54$, $P=.003$, g=0.54, respectively). Similar associations were not significant for the olanzapine group.

COMMENT

These results are consistent with previous studies in first-episode schizophrenia that reported changes in gray matter volume over time.[4-6,8,9] They also replicate findings of caudate volume increases associated with conventional antipsychotics but not atypical drugs.[30,31] The principal new finding of this study is the significant difference in the course and magnitude of these changes between patients treated with haloperidol, a conventional antipsychotic, and olanzapine, an atypical antipsychotic. Specifically, olanzapine was associated with less such change in brain volume observed during and in the aftermath of the first psychotic episode. These differences in volume change were highlighted by the comparison with healthy volunteers, which showed no significant reductions in gray matter volume and a trajectory similar to that of the olanzapine group.

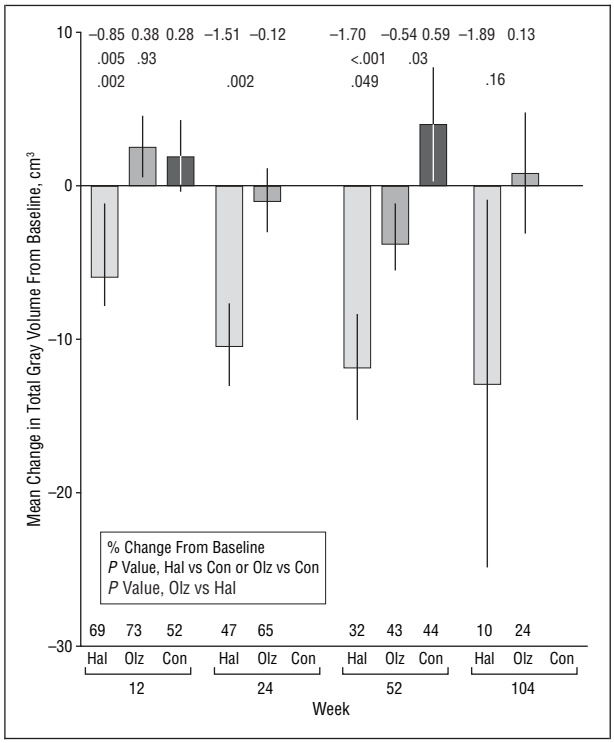

Figure 2. Mean changes in whole brain gray matter volumes by treatment group (from baseline to weeks 12, 24, 52, and 104) and healthy control group (from baseline to weeks 12 and 52). Hal indicates haloperidol; Olz, olanzapine; Con, controls; and limit lines, standard error.

These results are also consistent with previous studies that included first-episode patients with schizophrenia who predominantly received conventional antipsychotics.[4-6,8]

To our knowledge, the relative absence of such volume changes in olanzapine-treated patients has not been previously reported. The mean±SE maximum WBGM volume loss was –12.80±2.51 cm^3, or –1.9%, for the haloperidol group and –3.70±1.72 cm^3, or –0.5%, for the olanzapine group (Table 2). This magnitude of WBGM volume loss was less than that seen in elderly patients with Alzheimer disease (–5.03% per year) followed up over a similar timeframe[32] and comparable with the magnitude of change observed in previous schizophrenia studies.[8,9,13] The mean±SE maximum WBGM volume decreases in our haloperidol-treated patients were predominantly seen in the frontal (–7.56±2.04 cm^3, or –2.4%), parietal (–3.65±2.09 cm^3, or –2.9%), and temporal (–1.33±2.56 cm^3, or –1.1%) lobes, whereas little change was seen in the occipital lobes (Table 3). These results conform to the ROIs that have been implicated in the theoretical models of the pathophysiology of schizophrenia[33] and in previous postmortem[34] and in vivo imaging studies[1-3] and also are consistent with the cortical regions showing volume reductions in previous first-episode schizophrenia studies.[8,9,13]

While it appeared that most of the volume change occurred in the first 12 weeks of treatment, it is not clear whether progressive loss of gray matter was an acute phe-

The HGDH Study Group

The term *HGDH* is a naming convention used by the sponsor and has no significance. The HGDH study group consisted of the following people who participated in the design and execution of the study: Jeffrey A. Lieberman, MD, and Diana Perkins, MD, MPH, Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill; Charles B. Nemeroff, MD, PhD, Department of Psychiatry, Emory University School of Medicine, Atlanta, Ga; Franca Centorrino, MD, and Bruce Cohen, MD, PhD, McLean Hospital, Harvard Medical School, Belmont, Mass; Gary D. Tollefson, MD, PhD, Todd Sanger, PhD, and Mauricio Tohen, MD, DrPH, Lilly Research Laboratories, Indianapolis, Ind; Joseph P. McEvoy, MD, Cecil Charles, PhD, and Richard S. E. Keefe, PhD, John Umstead Hospital, Duke University Health System, Durham, NC; John Kuldau, MD, Department of Psychiatry, University of Florida, Gainesville; Alan I. Green, MD, Massachusetts Mental Health Center, Harvard Medical School, Boston; Anthony J. Rothschild, MD, and Jayendra K. Patel, MD, Department of Psychiatry, University of Massachusetts Medical Center, Worcester; Raquel E. Gur, MD, PhD, Department of Psychiatry, University of Pennsylvania Medical Center, Philadelphia; Robert B. Zipursky, MD, and Zafiris J. Daskalakis, MD, FRCPC, Department of Psychiatry, University of Toronto Faculty of Medicine, Toronto, Ontario; Stephen M. Strakowski, MD, Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio; Ira Glick, MD, Department of Psychiatry, Stanford University School of Medicine, Stanford, Calif; John De Quardo, MD, Department of Psychiatry, University of Michigan Medical Center, Ann Arbor; Rene S. Kahn, MD, PhD, University Hospital Utrecht, Utrecht, the Netherlands; Tonmoy Sharma, MD, Clinical Neuroscience Research Centre, Kent, England; and Robin Murray, MD, DSc, Institute of Psychiatry, London, England.

nomenon associated with the active phase of the illness and manifest symptoms, or, alternatively, the result of attrition in the extended follow-up phase of the study. A potential limitation of the high attrition rate is that the retained subset of patients may not be representative of the entire sample. However, a comparison of the baseline characteristics between the patients who completed 24, 52, and 104 weeks of the study and all patients who were randomized showed no meaningful differences. Moreover, a sensitivity analysis of 239 patients with at least baseline MRI, carrying forward observations (including baseline) when patients dropped out without obtaining follow-up MRIs, produced the same pattern of results, suggesting that the findings are not due to the particular pattern or differential nature of the attrition.

There are several possible explanations for the differences in the observed brain volume changes in the haloperidol- and olanzapine-treated patients. Although it is possible that these changes could be due to an artifact inherent in the image acquisition or analysis process, we do not believe that this was the case, as we could neither identify nor think of one that could produce this effect. Moreover, an artifactual process would presumably be random and not systematically affect only patients in one treatment group or the other. A second possibility is that treatments are not affecting brain structure per se but may alter blood flow and metabolism in the brain.[35-38] This possibility cannot be ruled out by the methods used for data acquisition in this study. A third explanation is a possible toxic effect of haloperidol that has been suggested to potentially induce oxidative stress and excitatory neurotoxicity.[39-41] In addition, caudate enlargement is known to be due to treatment effects of conventional drugs causing ultrastructural changes in striatal neurons[42-44] and alterations of dendritic morphology in cortical neurons.[45,46] However, in this study a relatively low dose of haloperidol was used (which may have accounted for the delayed and modest caudate volume enlargement that was seen), and there was no correlation between dose and brain volume change. An alternative interpretation of the brain volume changes observed in this study is that they reflect the underlying pathophysiology and progressive nature of schizophrenia.[14,15] Accordingly, if the changes in brain volume (that we and other investigators have found) reflect the pathological progression associated with schizophrenia, it is possible that olanzapine could have ameliorated this process, whereas haloperidol did not. Antipsychotic drugs have been suggested to have effects on neuroplasticity including synaptic remodeling and neurogenesis.[47] Specific atypical antipsychotic drugs (particularly clozapine and olanzapine) have been reported to have various actions that could enhance cellular resilience and ameliorate the pathophysiology of schizophrenia. These include the antagonism of the effects of *N*-methyl-D-aspartate receptor antagonists,[16,48] increased expression of trophic factors,[17-19] and stimulation of neurogenesis.[20-22] Consequently, these various actions of specific atypical antipsychotic drugs could be seen as ameliorating pathophysiologic effects on cell processes and synapses or enhancing their ability to withstand such insults. In this context, Wang and Deutch[49] recently reported that olanzapine treatment prevented decreases in the spine density of basilar dendrites on layers II/III and V of prefrontal cortex pyramidal neurons in rats in which lesions of cortical dopamine innervation were created by injection of 6-hydroxydopamine into the ventral tegmental area.

A consistent finding of postmortem studies in schizophrenia has been the decrease in cortical neuropil relative to tissue from control subjects.[50] These neuropathology findings are consistent with the gray matter volume reduction seen in MRI studies. Thus, subtle disease-associated loss of cell processes may be observed morphometrically as changes in gray matter volume.

The associations between greater decrease in WBGM volume and less improvement in neurocognitive functioning, and greater improvements on PANSS total and negative subscales with less increase in lateral ventricular volume indicate that treatment effects on brain volume and the behavioral pathology of the illness may be associated. These clinical and volumetric associations are also consistent with some[4,6,9,13] but not all[5] previous studies. Although these results must be confirmed, they suggest that a significant difference exists between a typical

antipsychotic (haloperidol) and an atypical agent (olanzapine) that is due to either a safety or efficacy advantage and reflected by a differential pattern of brain volume change and clinical response. Future clinical studies should attempt to verify whether the early stage of psychosis is associated with brain volume changes and whether antipsychotics can neurobiologically alter the course of the disease.

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