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Insight in first-episode psychosis

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ABSTRACT

Background. We report here a study examining the relationships between insight and psychopathology, cognitive performance, brain volume and co-morbid depression in 251 patients experiencing a first episode of psychosis, who were then randomly assigned to 2 years of double-blind treatment with either olanzapine or haloperidol.

Method. Repeated measures of insight were obtained at baseline and 12, 24, 52 and 104 weeks by the Insight and Treatment Attitudes Questionnaire (ITAQ).

Results. Older age, female gender and white ethnicity were associated with more insight. Higher total, positive, negative and general psychopathology scores on the Positive and Negative Syndromes Scale (PANSS) were associated with less insight. Higher depression scores were associated with more insight. Better neurocognitive function and large brain volumes were associated with more insight. More insight throughout the study was associated with longer time to medication non-adherence. However, baseline insight was not significantly related to the probability of discontinuing the study before 2 years. Insight improved significantly over the course of the study, but the improvement in insight was not significantly different between the two antipsychotic treatment groups.

Conclusions. Multiple factors contribute to insight. Patients experiencing a first episode of psychosis who have little insight are at increased risk of discontinuing their medication.

INTRODUCTION

Acknowledgment of illness and the need for treatment (insight) is frequently deficient among patients with psychosis (Amador & David, 2004). Because intact insight is somewhat associated with better treatment adherence (McEvoy, 2004), investigators have attempted to identify the factors that contribute to deficits in insight. In particular, multiple studies have addressed whether severity of psychosis, severity of cognitive impairment, brain volume and/or co-morbid depression are associated with insight (Amador & David, 2004). Most (Young *et al.* 1993; Kemp & Lambert, 1995; Macpherson *et al.* 1996*a*; McEvoy *et al.* 1996; Collins *et al.* 1997; Dickerson *et al.* 1997; Lysaker *et al.* 1997; Sanz *et al.* 1998; Young *et al.* 1998; Smith *et al.* 2000) but not all studies (McEvoy *et al.* 1993; Cuesta & Peralta, 1994; Kemp & David, 1996) have found that more severe psychosis is associated with lower levels of insight. Most (Young *et al.* 1993; Lysaker & Bell, 1994; David *et al.* 1995; Macpherson *et al.*

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1996*b*; Startup, 1996; Lysaker *et al*. 1997; Young *et al*. 1998; Mohamed *et al*. 1999; Laroi *et al*. 2000; Marks *et al*. 2000; Smith *et al*. 2000) but not all studies (McEvoy *et al*. 1993; Cuesta & Peralta, 1994; Cuesta *et al*. 1995; Collins *et al*. 1997; Dickerson *et al*. 1997; Sanz *et al*. 1998) have found that higher intelligence or better cognitive functioning is associated with higher levels of insight. Three studies (Takai *et al*. 1992; Flashman *et al*. 2000; Laroi *et al*. 2000) have found that larger brain volumes are associated with higher levels of insight, but one large study of first-episode psychosis did not find such a relationship (David *et al*. 1995). Most (Markova & Berrios, 1992; Amador *et al*. 1994; David *et al*. 1995; Kemp & Lambert, 1995; Sanz *et al*. 1998; Smith *et al*. 2000; Drake *et al*. 2004) but not all studies (e.g. Collins *et al*. 1997) have found that higher levels of co-morbid depression are associated with higher levels of insight.

In recent years, investigators have begun to study insight in patients experiencing a first episode of psychosis. Fennig *et al*. (1996) found that proportionately fewer patients experiencing a first episode of psychosis of schizophrenia had full insight than patients experiencing first episodes of bipolar disorder or other psychoses; the patients with schizophrenia were less likely to gain full insight with recovery as well. Patients experiencing a first episode of schizophrenia are significantly less likely to have good insight than patients who have had multiple episodes of schizophrenia (Thompson *et al*. 2001). It is not surprising then that approximately 60% of patients discontinue their prescribed treatment within 1 year of experiencing their first episodes of schizophrenia (Novak-Grubic & Tavcar, 1999; Verdoux *et al*. 2000; Coldham *et al*. 2002).

More severe psychopathology and more substance misuse (Verdoux *et al*. 2000; Coldham *et al*. 2002), less insight (Mutsatsa *et al*. 2003), and the absence of a family member involved in their treatment (Coldham *et al*. 2002) characterized patients who discontinued their treatment shortly after a first psychotic episode. Patients who required involuntary commitment for treatment of their first psychotic episodes are significantly more likely to require involuntary commitment for treatment of subsequent episodes (Fennig *et al*. 1999).

Higher levels of depression were associated with more insight in first-episode psychosis (Drake *et al*. 2004). However, first-episode patients with poor insight had decreased right dorsolateral prefrontal cortex volumes, and higher levels of perseverative errors on the Wisconsin Card Sorting Test, than first-episode patients with good insight (Shad *et al*. 2004).

Here we report a study examining the relationships between insight and psychopathology, cognitive performance, brain volume and co-morbid depression in a large sample of patients experiencing first-episode psychosis, who were then randomly assigned to 2 years of double-blind treatment with either olanzapine or haloperidol. We address four questions of interest to clinicians: (1) in first-episode patients, is insight related to psychopathology, cognitive performance, brain volume and/or co-morbid depression; (2) is insight associated with medication adherence over the course of the trial; (3) is baseline insight predictive of survival in treatment; and (4) does treatment with olanzapine *versus* haloperidol differentially affect insight over 2 years of treatment?

METHOD

Data were collected as part of a 2-year randomized, double-blind clinical trial that compared the efficacy and safety of olanzapine with that of haloperidol in patients experiencing a first episode of DSM-IV schizophrenia, schizophreniform or schizo-affective disorder. The trial was conducted from March 1997 to July 2001 at 14 academic centers (see HGDH Research Group listing). A detailed description of the study methods is available in an earlier publication (Lieberman *et al*. 2003).

Subjects

This study involves 251 of the 263 randomized patients who had baseline insight information recorded. These patients were aged 16–40 years, met DSM-IV diagnostic criteria prior to age 35 years, and could not have been ill more than 5 years. If a prior psychotic episode had remitted, or if patients had prior antipsychotic drug treatment for more than 16 cumulative weeks, they were not considered first-episode and were excluded. Patients had to have experienced active psychotic symptoms [scored $\geqslant 4$ on at least

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two or scored $\geqslant 5$ on at least one of the Positive and Negative Syndromes Scale (PANSS; Kay *et al*. 1987) psychosis items (P1, P2, P3, P5 or P6), and scored $\geqslant 4$ on the Clinical Global Impressions-Severity scale (CGI-S; Guy, 1976)] in order to participate. Patients had to have a pre-morbid IQ $\geqslant 70$ to participate. In order not to compromise safety in a randomized trial, patients could not be at serious suicidal risk.

Each patient (or a patient's authorized legal representative) had the nature of the study explained and signed an informed consent document. Patients underwent a 2–14-day placebo wash-out period, after which they were randomized to treatment with olanzapine (5–20 mg/day) or haloperidol (2–20 mg/day). Baseline study assessments were completed prior to randomization. Follow-up assessments were completed for up to 2 years, with weekly assessments for the first 6 weeks, biweekly assessments for the next 6 weeks, and monthly assessments thereafter. Longitudinal analyses used only that subsample that returned for at least one post-baseline assessment.

Assessments

Insight was measured at baseline, and 12, 24, 52 and 104 weeks by the Insight and Treatment Attitudes Questionnaire (ITAQ; McEvoy *et al*. 1989). The ITAQ consists of 11 items each scored on a 0–2 scale that measures a patient's insight into his/her psychiatric illness and need for treatment. The items are summed and the total, which can range from 0 to 22, is used as a measure of insight. Higher scores reflect higher insight. Psychopathology was assessed at baseline by the PANSS (Kay *et al*. 1987) total and subscale scores, and the CGI-S, and depression was measured by the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979).

Baseline cognitive functioning was reflected by the principal component score derived by combining scores from tests of verbal fluency, attention, verbal memory and learning, visuomotor speed, working memory, and motor speed included in the primary neurocognitive battery (Keefe *et al*. 2004). This single factor accounted for most of the variance in the neurocognitive variables and we wanted to minimize type I statistical error. We present analyses involving neurocognitive function at baseline only, allowing us to calculate principal component scores for the larger sample of patients ($n=203$) who had at least baseline neurocognitive testing.

The magnetic resonance imaging (MRI) protocol included three-dimensional T1-weighted, inversion recovery-prepared spoiled gradient-recalled acquisition in steady-state images ($0{\cdot}94 \times 0{\cdot}94 \times 1{\cdot}50$ mm, axial direction) and contiguous proton density and T2-weighted fast spin–echo images ($0{\cdot}94 \times 0{\cdot}94 \times 3{\cdot}00$ mm, axial slicing direction). Volumes of gray and white matter were extracted.

To assess medication adherence, at each study visit, the number of pills taken/prescribed since the preceding visit was recorded. These numbers were obtained from pill counts as well as from questioning the subject.

Statistical methods

To assess relationships between baseline insight and baseline psychopathology, cognitive performance, brain volumes, co-morbid depression and demographic variables, we first fit several linear models, each with the baseline ITAQ total score as the outcome and one of the following baseline measures as a predictor: PANSS total, PANSS positive total, PANSS negative total, PANSS general psychopathology, MADRS total, CGI-S, neurocognitive principal component,whole brain volume (gray + white), whole brain gray volume, whole brain fluid volume, whole brain white volume, age in years, duration of previous antipsychotic use in days, duration of illness (time from disease onset to study enrollment) in weeks, gender, ethnicity (black, white, other), diagnosis, and antipsychotic naivety (yes/no). We included investigator as a covariate in these models. We also included age, gender and ethnicity as covariates in models containing any brain volume as a predictor, noting the possible confounding roles of these variables. In addition, we performed a backwards elimination procedure to build a regression model for baseline insight using all the above baseline variables of interest. Because of collinearity between whole brain volume and whole brain gray and whole brain white volumes and between PANSS total and the PANSS subscales, we did not include whole brain volume or the PANSS general psychopathology subscale in this model. At each step

Table 1. *Demographics over all patients and by treatment group*

Variable	All patients ($n=251$)	Olanzapine ($n=127$)	Haloperidol ($n=124$)	p value
Age (years), mean (S.D.)	23·86 (4·71)	23·62 (4·63)	24·10 (4·81)	0·4395[a]
Duration of previous antipsychotic use (weeks), mean (S.D.)	6·06 (10·85)	5·40 (6·89)	6·79 (13·96)	0·9359[a,c]
Duration of illness (weeks), mean (S.D.)	62·47 (59·79)	52·95 (53·27)	72·21 (64·58)	0·0143[a]
Male, *n* (%)	204 (81·27)	100 (78·74)	104 (83·87)	0·3337[b]
Female, *n* (%)	47 (18·73)	27 (21·26)	20 (16·13)	
Caucasian, *n* (%)	133 (52·99)	64 (50·39)	69 (55·65)	0·5543[b]
African descent, *n* (%)	93 (37·05)	48 (37·80)	45 (36·29)	
Other, *n* (%)	25 (9·96)	15 (11·81)	10 (8·06)	
Schizophrenia, *n* (%)	148 (58·96)	68 (53·54)	80 (64·52)	0·1974[b]
Schizophreniform disorder, *n* (%)	77 (30·68)	45 (35·43)	32 (25·81)	
Schizo-affective disorder, *n* (%)	26 (10·36)	14 (11·02)	12 (9·68)	
Previous antipsychotic use, *n* (%)	186 (74·40)	96 (75·59)	90 (73·17)[d]	0·6670[b]
Previous antipsychotic use no, *n* (%)	64 (25·60)	31 (24·41)	33 (26·83)	
PANSS total, mean (S.D.)	80·48 (14·65)	80·52 (14·19)	80·44 (15·16)	0·9535[a]
PANSS positive, mean (S.D.)	21·49 (4·48)	21·35 (4·60)	21·65 (4·38)	0·4949[a]
PANSS negative, mean (S.D.)	19·41 (5·79)	19·36 (5·69)	19·47 (5·91)	0·9646[a]
PANSS general psychopathology, mean (S.D.)	39·57 (8·39)	39·81 (8·29)	39·33 (8·51)	0·6966[a]
CGI severity, mean (S.D.)	4·52 (0·62)	4·52 (0·60)	4·52 (0·63)	0·9632[a]
MADRS total, mean (S.D.)	11·51 (7·41)	11·58 (7·82)	11·43 (7·00)	0·9265[a]

PANSS, Positive and Negative Syndromes Scale; CGI, Clinical Global Impressions; MADRS, Montgomery–Asberg Depression Rating Scale.

[a] Two-sided Wilcoxon test using normal approximation and continuity correction; tests for therapy difference.

[b] Fisher's exact test; tests for therapy difference.

[c] Calculated only for patients with any previous antipsychotic use [$n=184$, olanzapine ($n=96$), haloperidol ($n=88$)].

[d] Dopamine-receptor blocking antipsychotic use is unknown for one haloperidol patient.

of the elimination, the variable with the least significant type III F test was removed. We continued removing variables one at a time, until all predictors in the model were significant at a $p \leqslant 0{\cdot}10$ level. We report the model for baseline insight resulting from this backwards elimination procedure.

To evaluate whether insight over the course of the study was predictive of non-adherence, we fit a Cox proportional hazards for time to non-adherence with therapy, ITAQ total, and investigator as predictors. Perkins *et al.* (2006) gives detailed reasoning for the choice of this type of analysis strategy and choice of outcome for modeling non-adherence. Following the protocol definition of non-adherence, a subject was considered non-adherent if they did not take any medication for seven or more consecutive days. The date of non-adherence was defined at the first day of the non-adherent period. If a subject never met criteria for non-adherence, they were censored at the date of study discontinuation. In this analysis, insight was treated as a time-dependent covariate, so that baseline insight was a predictor for time to non-adherence up to 12 weeks, 12-week insight was a predictor for time to non-adherence up to 24 weeks, 24-week insight was a predictor for time to non-adherence up to 52 weeks, and 52-week insight was a predictor for time to non-adherence up to 104 weeks.

To assess the relationship between baseline insight and study discontinuation up to 2 years, we fit a logistic regression model with discontinuation before 2 years (yes/no) as the outcome, and investigator, treatment group, and baseline ITAQ total score as predictors, plus an intercept term. We also fit a Cox proportional hazards regression model for time to study discontinuation up to 2 years, using the same covariates.

To evaluate whether insight changed differentially over the course of the study for olanzapine *versus* haloperidol subjects, we fit a repeated-measures model with the ITAQ total score as the outcome, and treatment group, time, time squared, treatment group × time interaction, treatment group × time squared interaction, duration of illness and investigator as fixed effects. We included duration of illness as a covariate in this model as this was significantly different for the two therapy groups.

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Table 2. *Associations between baseline insight and baseline variables (partial correlations for continuous variables and least squares means for discrete variables)*

Baseline variable	*n*	Partial correlation[a]	*p* value[b]
PANSS total	251	−0·2943	<0·0001
PANSS positive total	251	−0·2210	0·0006
PANSS negative total	251	−0·2817	<0·0001
PANSS general psychopathology	251	−0·2138	0·0009
MADRS total	251	0·2091	0·0011
CGI severity	251	−0·1832	0·0045
Neurocognitive principal component	203	0·2231	0·0019
Whole brain volume (gray + white)	226	0·1530	0·0267
Whole brain gray volume	226	0·1368	0·0477
Whole brain fluid volume	226	−0·0619	0·3722
Whole brain white volume	226	0·1627	0·0183
Lateral ventricular volume	226	−0·0068	0·9218
Age (years)	251	0·1562	0·0156
Duration of previous antipsychotic use (days)	251	0·0866	0·1820
Duration of illness (weeks)	251	0·0904	0·1636
		LS means (S.E.)[c]	
Gender female	251	14·914 (0·792)	0·0205
Gender male		12·898 (0·426)	
Ethnicity black	251	12·659 (0·644)	0·0021
Ethnicity white		14·306 (0·516)	
Ethnicity other		10·487 (1·100)	
Diagnosis schizoaffective disorder	251	14·001 (1·108)	0·6865
Diagnosis schizophrenia		13·037 (0·508)	
Diagnosis schizophreniform disorder		13·486 (0·660)	
Antipsychotic naive no	251	13·692 (0·729)	0/4984
Antipsychotic naive yes		13·136 (0·447)	

PANSS, Positive and Negative Syndromes Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinical Global Impressions; LS, least squares.

[a] Correlation between baseline insight and baseline variable, adjusting for investigator.

[b] *p* value from a type III *F* test for the baseline variable in a model with baseline insight as outcome and baseline variable and investigator as predictors.

[c] Estimated least squares means for each category of the baseline variable in a model with baseline insight as outcome and the baseline variable and investigator as predictors.

Most of the improvement in clinical trials of antipsychotic medications occurs early; this produces a curvilinear relationship between time and the response variable. Fitting a quadratic model in time enables us to model the curve.

RESULTS

Table 1 presents demographic information over all subjects and by therapy group. Table 2 presents partial correlations, least squares means and *p* values describing relationships between baseline insight and baseline psychopathology, depression, cognitive performance, brain volume and demographic variables.

Among the baseline demographic variables, age, gender and ethnicity were significantly related to baseline insight ($p=0{\cdot}0156$, $p=0{\cdot}0205$, $p=0{\cdot}0021$). Older age, female gender and white ethnicity were associated with more insight. Every one of the baseline psychopathology measures was significantly related to baseline insight (all $p<0{\cdot}005$). Higher PANSS total, PANSS positive, negative and general psychopathology subscale, and CGI severity scores are associated with less insight (partial correlations: −0·294, −0·221, −0·282, −0·214, −0·183). Additionally, higher MADRS total scores are associated with more insight (partial correlation: 0·209).

Baseline neurocognitive principal component score is significantly related to baseline insight ($p=0{\cdot}0019$). Better neurocognitive function is associated with more insight (partial correlation: 0·223).

Among the baseline MRI volume measurements, whole brain volume, whole brain gray volume and whole brain white volume are significantly associated with baseline insight after adjusting for age, gender and ethnicity (all

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Table 3. *Associates between baseline insight and baseline variables adjusting for other baseline variables significantly related to insight*

Baseline variable	Partial correlation[a]	*p* value[b]
PANSS total	−0·3805	<0·0001
MADRS total	0·3745	<0·0001
Whole brain fluid volume	−0·2114	0·0059
Whole brain white volume	0·2036	0·0081
Duration of illness	0·1460	0·0590
	LS mean[c]	
Ethnicity		
Black	12·808 (0·787)	0·0201
White	13·492 (0·635)	
Other	9·861 (1·250)	

PANSS, Positive and Negative Syndromes Scale; MADRS, Montgomery–Asberg Depression Rating Scale; LS, least squares.

[a] Correlation between baseline insight and baseline variable, adjusting for all other baseline variables and investigator.

[b] *p* value from a type III *F* test for the baseline variable in a model with baseline insight as outcome and all other baseline variables and investigator as predictors.

[c] Estimated least squares means for each category of the baseline variable in a model with baseline insight as outcome and all other baseline variable and investigator as predictors.

$p<0·05$). Larger brain volumes are associated with more insight (partial correlations: 0·153, 0·137, 0·163).

More insight throughout the study was associated with longer time to non-adherence (hazard ratio = 0·962, $p=0·0076$). The hazard ratio compares the likelihood of becoming non-adherent at each assessment point for two patients with a one-point difference in ITAQ score; the patient with the higher score is 0·962 times as likely to become non-adherent as the patient with the lower ITAQ score. Adjusting for insight, haloperidol-treated patients became non-adherent faster than olanzapine-treated (hazard ratio = 1·533, $p=0·0420$).

Table 3 describes relationships between baseline insight and the baseline predictors remaining after the backwards elimination model building procedure. This procedure fit a model including all baseline variables of interest and sequentially removed any variable not significantly related to baseline insight when the other baseline variables were present in the model. The table provides partial correlations between baseline insight and each continuous predictor in the model and least squares means for categorical predictors. It also gives *p* values for type III *F* tests of the significance of each variable in the model. Following the elimination procedure, ethnicity, whole brain white volume, whole brain fluid volume, MADRS total score, and PANSS total score remained significantly associated with baseline insight ($p=0·0201$, $p=0·0081$, $p=0·0059$, $p<0·0001$, $p<0·0001$). Higher PANSS total and whole brain fluid volume remained associated with less insight (partial correlations: −0·3805, −0·2114). Higher MADRS total, total white volume, and duration of illness remained associated with more insight (partial correlations: 0·3745, 0·2036, 0·1460).

After adjusting for baseline insight, haloperidol-treated patients were significantly more likely than olanzapine-treated patients to discontinue the study before 2 years ($p=0·0177$). However, baseline insight was not significantly related to the probability of discontinuing the study before 2 years ($p=0·6223$). When considering time to discontinuation up to 2 years, after adjusting for baseline insight, haloperidol-treated patients discontinued the study earlier than olanzapine-treated patients ($p=0·0110$). However, baseline insight was not significantly related to the time to discontinuation up to 2 years ($p=0·3900$).

Table 4 gives least squares means for ITAQ total by treatment group at each time of insight measurement as well as *p* values for type III *F* tests of whether these differ by treatment group. There was a significant increase in insight over the course of the study ($p=0·0004$). The change in insight was not significantly different between the two antipsychotic treatment groups ($p=0·6158$).

DISCUSSION

In agreement with most previous studies, we found that higher levels of insight are associated with less schizophrenic psychopathology, better cognition, larger brain volumes and higher levels of depression. Although correlation does not imply causality, it is tempting to speculate that psychosis, cognitive impairment and decreased brain volume interfere with the capacity to evaluate one's condition realistically.

Patients with more insight as measured by the ITAQ had more depression as measured by the MADRS. Depression is associated with more accurate self-appraisal in the general population and in patients with a variety of

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Table 4. *Estimated ITAQ total over time by therapy*

Treatment group	Baseline		Week 12		Week 24		Week 52		Week 104	
	LS mean (S.E.)	*p* value[a]	LS mean (S.E.)	*p* value[a]	LS mean (S.E.)	*p* value[a]	LS mean (S.E.)	*p* value[a]	LS mean (S.E.)	*p* value[a]
Olanzapine	13·544 (0·544)	0·3524	14·476 (0·507)	0·1213	15·244 (0·563)	0·0966	16·400 (0·730)	0·1197	16·183 (1·033)	0·4516
Haloperidol	12·853 (0·499)		13·348 (0·513)		13·782 (0·667)		14·552 (0·928)		15·084 (1·023)	

ITAQ, Insight and Treatment Attitudes Questionnaire; LS, least squares.
[a] Type III *F* test; compares treatment groups.

psychiatric illnesses (Cassidy *et al*. 2001). It is unclear whether depression removes a healthy glossing over of deficits or whether an accurate self-appraisal results in disappointment and depression. For subjects with high insight, clinicians may need to be more sensitive to depression and its possible treatment.

Individuals of African descent had slightly lower ITAQ scores than whites, in keeping with the findings of some (e.g. Perkins & Moodley, 1993; Johnson & Orell, 1996) but not all (e.g. David et al. 1995) studies. A mixed group of individuals of 'other' ethnicities (mostly Asian and Hispanic) had even lower scores. White *et al*. (2000) found that foreign birth explained more than ethnicity about lower insight ratings among non-white populations. Cultural differences in illness explanation and clinician–patient interaction may confound the assessment of insight, and it may be more difficult as members of non-majority ethnic groups may be less able to incorporate the additional challenge of mental illness into their self-images (Kirmayer *et al*. 2004).

In this large sample of patients with first-episode psychoses, we found that ethnicity, age, gender, cognition, brain volume, psychotic psychopathology and depression are independently associated with insight, each weakly, but together explaining 42% of the variance in insight. Insight did contribute to medication adherence over time, as has been reported by others (McEvoy, 2004), even in this study setting, where patients and their families had frequent contact with research staff who had great interest in maintaining the patients in treatment and who provided free care to the patients.

Baseline levels of insight did not predict survival in treatment. Patients who participated in this clinical trial, and their families, received substantially more attention than they might receive in standard clinical treatment settings, and this may have overwhelmed any effect insight alone would have on survival.

Although pharmacotherapy with olanzapine was associated with longer persistence in treatment (Lieberman *et al*. 2005), better neurocognitive function (Keefe *et al*. 2006) and potential neuroprotective effects over time (Lieberman *et al*. 2005), relative to treatment with haloperidol, its advantage did not extend to a differentially greater improvement in insight.

This study, using well-established measures in a large sample of patients with first-episode psychosis, serves to confirm and solidify knowledge about certain variables associated with insight. It is always an issue for studies such as this that the patients who agree to participate are probably more compliant and insightful than those who refuse. The high baseline levels of insight may reflect the selection of patients, as well as the difficulties in assuring rating consistency on an unfamiliar scale across a large number of trial sites. Both the patients and their family members may have been more treatment adherent because treatment was provided without charge. Finally, we used a unidimensional measure of insight and a limited measure of treatment adherence (largely based on pill counts), and we collected scant data regarding the ethnic and cultural factors affecting our sample.

APPENDIX. The HGDH Study Group

The Group consists of: Drs Jeffrey Lieberman and Diana Perkins, University of North Carolina, Chapel Hill, NC; Dr Charles B. Nemeroff, Emory University School of Medicine, Atlanta; Drs Franca Centorrino and Bruce Cohen, McLean Hospital, Harvard

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DECLARATION OF INTEREST

None.

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