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Impact on Intracortical Myelination Trajectory of Long Acting Injection Versus Oral Risperidone in First-Episode Schizophrenia

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Abstract

Context—Imaging and post-mortem studies suggest that frontal lobe intracortical myelination is dysregulated in schizophrenia (SZ). Prior MRI studies suggested that early in treatment of SZ, antipsychotic medications initially increase frontal lobe intracortical myelin (ICM) volume, which subsequently declines prematurely in chronic stages of the disease. Insofar as the trajectory of ICM decline in chronic SZ is due to medication non-adherence or pharmacokinetics, it may be modifiable by long acting injection (LAI) formulations.

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Contributors

George Bartzokis and Keith Nuechterlein designed the study and wrote the protocol.

Jim Mintz and Po Lu undertook the statistical analysis.

Keith Nuechterlein, Joseph Ventura, Nicole Detore, Laurie Casaus, John Luo, and Kenneth Subotnik recruited and supervised the assessments of the subjects.

Erika Raven, Chetan Amar, and Alexander Couvrette performed and managed the image analyses.

George Bartzokis, Po Lu, and Jim Mintz wrote the first draft of the manuscript.

George Bartzokis, Keith Nuechterlein, and Kenneth Subotnik edited and revised the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of Interest

All other authors declare that they have no conflicts of interest.

Objectives—Assess the effect of risperidone formulation on the ICM trajectory during a six-month randomized trial of LAI (RLAI) versus oral (RisO) in first-episode SZ subjects.

Design—Two groups of SZ subjects (RLAI, N=9; and RisO, N=13) matched on pre-randomization oral medication exposure were prospectively examined at baseline and six months later, along with 12 healthy controls (HCs). Frontal lobe ICM volume was assessed using inversion recovery (IR) and proton density (PD) MRI images. Medication adherence was tracked.

Main outcome measure—ICM volume change scores adjusted for the change in the HCs.

Results—ICM volume increased significantly ($p=.005$) in the RLAI and non-significantly ($p=.39$) in the RisO groups compared to the healthy controls. A differential between-group treatment effect was at a trend level ($p=.093$). SZ subjects receiving RLAI had better medication adherence and more ICM increases (chi-square $p<.05$).

Conclusions—The results suggest that RLAI may promote ICM development in first-episode SZ patients. Better adherence and/or pharmacokinetics provided by LAI may modify the ICM trajectory. In vivo MRI myelination measures can help clarify pharmacotherapeutic mechanisms of action.

Keywords

antipsychotic; medication; dopamine; second generation; atypical; myelin; white matter; gray matter; oligodendrocyte; development; aging

INTRODUCTION

Antipsychotic treatments result in high levels of symptom remission, ranging from 70 to 87%, in first-episode schizophrenia (SZ) patients during the first year of treatment (Boter et al, 2009; Emsley et al, 2007; Lieberman et al, 1993; Nuechterlein et al, 2006; Robinson et al, 1999; Robinson et al, 2004; Saravanan et al, 2010). Subsequently, recurrent episodes, frequently associated with poor adherence (Subotnik et al, 2011), are often followed by a deteriorating clinical trajectory (Lieberman, 2006) and a reduced responsiveness to antipsychotics (“treatment resistance”) (Kane et al, 1988; Lieberman et al, 2001a; Lieberman et al, 2001b). Long-acting injection (LAI) formulations of antipsychotics can improve clinical outcomes (reviewed in Keith, 2009); however, the mechanism through which LAI medications improve outcomes remains unknown.

Myelination involves wrapping axons with a highly specialized lipid membrane that increases transmission speed of action potentials over 100 fold (O'Brien and Sampson, 1965; Rouser et al, 1972; Saher et al, 2005). We have proposed that dysregulation of the normal myelination trajectory may contribute to the etiology of schizophrenia (Bartzokis, 2002; Bartzokis, 2011; Bartzokis, 2012) and that deficient myelination may lead to the functional deterioration and “treatment resistance” observed in chronic SZ (Bartzokis and Altshuler, 2005; Bartzokis and Altshuler, 2003; Bartzokis et al, 2012). Furthermore, we recently proposed that antipsychotic medications may promote white matter development and specifically intracortical myelin (ICM) as one of their mechanisms of action (Bartzokis et al, 2012).

Post-mortem studies of chronic SZ support the existence of an ICM deficit with cytology data revealing *cortical* glial deficits in SZ due primarily to lower numbers of oligodendrocytes and myelin stain data confirming an ICM deficit that seems particularly prominent in the frontal lobes (Beasley et al, 2009; Chambers and Perrone-Bizzozero, 2004; Flynn et al, 2003; Hof et al, 2002; Hof et al, 2003; Parlapani et al, 2009; Schmitt et al, 2009; Uranova et al, 2011; Uranova et al, 2004; Vostrikov et al, 2007) (reviewed in Bartzokis,

2011). Imaging studies that assessed white matter volume (Bartzokis et al, 2012; Bartzokis et al, 2003; Cocchi et al, 2009; Ho et al, 2003; Whitford et al, 2007) (reviewed in Bartzokis, 2002; Bartzokis, 2011) provided consistent evidence of a deficient myelination trajectory that, unlike the rising trajectory of healthy individuals, ceases its development during early adulthood. These divergent trajectories are consistent with post-mortem cytology data that show significant age-related increases in intracortical oligodendrocyte numbers in normal individuals and decreasing numbers in SZ (Vostrikov and Uranova, 2011; Vostrikov et al, 2007). An ICM deficit is also consistent with loss of cortical neuropil resulting in increased neuronal density (Bartzokis and Altshuler, 2005; Selemon et al, 1995; Selemon et al, 1998), decreased expression of myelin genes revealed in proteome and transcriptome analyses of cortex (Aston et al, 2004; Hakak et al, 2001; Katsel et al, 2005) (reviewed in Martins-de-Souza, 2010) and the prominence of myelin and myelination signaling genes as candidates for genetic components of SZ (Alaerts et al, 2009) (reviewed in Jaaro-Peled et al, 2009; Le-Niculescu et al, 2007).

The dysregulation in ICM development is hypothesized to result in an insufficient capacity to maintain temporal synchrony of the brain's widely distributed functional neural networks, which in turn may contribute to the heterogeneity of symptoms and cognitive impairments that characterize disorders such as schizophrenia (Bartzokis, 2002; Bartzokis, 2012; Spencer et al, 2004). An MRI method to estimate ICM in vivo has been developed and used to examine the effect of antipsychotic medications on ICM (Bartzokis et al, 2009). The method combines distinct tissue contrasts provided by inversion recovery (IR) and proton density (PD) MRI images. Myelin membranes have the highest cholesterol content of any brain tissue (O'Brien and Sampson, 1965; Rouser et al, 1972; Saher et al, 2005). IR images are most sensitive to cholesterol concentrations (Koenig, 1991) and provide optimal contrast for quantifying myelination (Barkovich et al, 1992; Valk and van der Knaap, 1989; van der Knaap and Valk, 1990). Thus, IR images track myelination into the cortex best, while PD images do not and ICM can be measured by the tissue between the gray/white matter borders defined by IR and PD images (Figure 1). The lifetime myelination trajectory of normal individuals observed in vivo with IR sequences corresponds very well to published post-mortem data showing that peak frontal lobe myelination is reached in the fifth decade of life, thereby providing validation of the imaging method of tracking myelination (Bartzokis et al, 2001; Bartzokis et al, 2012; Kemper, 1994).

In a prior cross-sectional study we observed that, very early in treatment, both typical (first generation) and atypical (second generation) antipsychotics increased frontal lobe ICM volume above that of healthy controls (Bartzokis et al, 2009). In a subsequent *prospective* study, we observed that in first-episode SZ subjects risperidone delivered as LAI could increase overall frontal lobe myelinated white matter volume compared to the oral mode of delivery (Bartzokis et al, 2011). In the current study we extend our prior cross sectional observation that antipsychotic treatments may increase ICM in first-episode SZ by measuring ICM volumes from existing imaging data from the prospective and randomized trial of oral risperidone (RisO) versus risperidone Consta long-acting injection (RLAI) (Bartzokis et al, 2011).

METHODS

Subjects

The MRI data were collected from schizophrenic subjects who were participating in a randomized controlled trial of RisO vs. RLAI in the Developmental Processes in Schizophrenia Disorders Project, conducted at the UCLA Aftercare Research Program (Nuechterlein et al, 1992; Nuechterlein et al, 2008). The first psychotic episode for the SZ subjects began within the last two years (median interval from onset of first episode until

study entry was 6 months (SD=5.9)). A DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type, was established using the Structured Clinical Interview for DSM-IV by diagnosticians with demonstrated inter-rater reliability (Nuechterlein et al, 2008; Ventura et al, 1998). Throughout this article the schizoaffective subgroup is subsumed under the schizophrenia diagnosis unless otherwise specified.

All subjects signed written informed consents approved by the local Institutional Review Board prior to study participation, after receiving written and oral information about the study. Exclusion criteria were as follows: no significant use of drugs or alcohol in the past year (amount of use did not meet DSM-IV criteria for alcohol/substance dependence or abuse); no history or gross evidence of central nervous system impairment or any history of neurological disorder, including head trauma with loss of consciousness for greater than 15 minutes; no history of chronic medical conditions that are likely to result in structural brain abnormalities (i.e., stroke, transient ischemic attack, seizures, hypertension, diabetes, etc.) (Nuechterlein et al, 2008).

Forty-five patients from the randomized controlled trial in the Developmental Processes in Schizophrenia Disorders Project were recruited for this MRI study. At entry into the Aftercare Research Program, all subjects were taking oral antipsychotic medications: risperidone 52%, olanzapine 24%, quetiapine 20%, and ziprasidone 4%. In order to establish a common baseline treatment, the 48% of subjects who were not already taking RisO were cross-tapered from their initial antipsychotic medication to RisO. All subjects were on RisO as the sole antipsychotic medication for a minimum of 10 weeks prior to baseline MRI assessment.

When participants reached the randomization point, treatment arm assignment was determined using a random number table. All treatment was open-label. Assignment was to treatment with oral risperidone (RisO) or risperidone long-acting injectable (RLAI). The initial two injections of RLAI were 25 mg every two weeks. Thereafter, dosage of RLAI was based on clinical need. The RisO or RLAI dose was optimized by the treating psychiatrists based on the clinical response of each patient. This resulted in a mean dose of 2.9 mg (SD=1.8, range 1 to 7.5 mg) for the RisO group and 26.4 mg (SD=4.2, range 12.5 to 37.5 mg) (modal dose 25 mg) for RLAI group. These average doses are in line with the equivalent doses for switching from RisO to RLAI (3 mg RisO and 25 mg RLAI) (Bai et al, 2007). This MRI study component had an attrition rate of 33% between the baseline and the 6-month point. Of these, eight were lost to follow-up (four refused treatment and testing, three had difficulty attending clinic due to personal/family issues, and one developed a substance abuse problem and was referred to a dual diagnosis program) and seven were switched to a different medication before study end point. There was no difference in MRI study attrition rate between RLAI and RisO groups ($\chi^2=.19$, $p=.66$), or in the diagnosis of schizoaffective disorder (18% and 15%, respectively; $\chi^2=.034$, $p=.86$). Similarly, there were no significant differences in the demographics (age, gender, race) of the dropouts compared to the subjects who completed both MRIs on assigned medication (χ^2 and t-statistics, $p>.24$).

Our prior cross sectional data that examined white matter volume as a function of length of antipsychotic treatment showed a non-linear (quadratic – “inverted U”) trajectory that peaked at 12 months after the initiation of treatment, followed by a decline compared to normal controls (Bartzokis et al, 2012). This non-linear trajectory as a function of medication exposure made it imperative that the RisO and RLAI groups were closely matched for pre-randomization medication exposure. We therefore set an a priori limit on the maximum difference in pre-randomization exposure to antipsychotic medications between the RisO and RLAI groups of one month. This set a minimum pre-baseline

medication exposure of 4.3 months, which excluded three participants with shorter exposures. On the upper end of exposures one subject was excluded because of pre-randomization medication exposure that was almost 4 SDs longer than the entire sample mean. Excessive motion artifact excluded one subject as did the discovery of exposure to LAI antipsychotic of a subject randomized to RisO, and two SZ and two HC subjects were excluded due to structural artifacts on the PD images. The average exposure to antipsychotic medications at the baseline scan for the twenty-two SZ subjects included in the analysis was 7.35 months (range 4.27 to 14.20 months) and the two treatment groups did not differ on this parameter ($p=.10$) (Table 1). The two groups were not statistically different in demographic variables except for racial/ethnic composition which differed between the groups ($\chi^2=7.82$, $df=3$, $p=.05$). The RisO group was comprised of 4 (31%) African Americans, 5 (38%) Hispanics, and 4 (31%) Caucasians while the RLAI group was comprised of 4 (44%) African Americans, 2 (22%) Hispanics, 3 (33%) Asians, and no Caucasians. There was no difference in the distribution of the 4 schizoaffective individuals in the two treatment groups ($\chi^2=0.17$, $df=1$, $p=.683$).

Our comparison group consisted of 12 healthy control (HC) subjects. At a minimum, each healthy subject completed a semi-structured clinical interview based on written standardized questions to assess the history of medical, psychiatric, and substance dependence disorders. Selection criteria were as follows: no evidence of significant current or past psychiatric diagnosis or substance dependence based on DSM-IV criteria; no significant use of drugs or alcohol in the past year (amount of use did not meet DSM-IV criteria for alcohol/substance dependence or abuse); no history or gross evidence of central nervous system impairment or any history of neurological disorder or head trauma with loss of consciousness for greater than 15 minutes; no history of chronic medical conditions likely to result in structural brain abnormalities (i.e., stroke, transient ischemic attack, seizures, hypertension, diabetes, etc.); and self-report that no first-degree relative has been treated for a major psychiatric disorder. These subjects were matched for demographic characteristics to the SZ cohort (HC vs. SZ: age 24.2 vs. 25.4, $p=.46$; race, $p=.12$; and gender 8m/4f vs. 16m/6f, $p=.72$) with the exception of education (12.3 vs. 15.8 years, $p<.0001$).

Adherence

A dimension of adherence to risperidone across the long-acting injectable and oral groups was calculated on a 1–5 scale based on timeliness of injections for injectable medication, and on pill counts, patient reports, plasma levels, psychiatrist judgments, and MEMS® caps data for oral medication (Subotnik et al, 2011). Thus, the patient's compliance to medication from baseline to endpoint was rated on this Likert scale with 1 being perfect compliance and 5 being the worst compliance.

Psychiatric Symptoms

The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) were designed to assess negative and positive symptoms of psychopathology, principally those that occur in schizophrenia. The negative symptoms assessed by the SANS include flat affect, alogia, apathy, anhedonia, and inattention; the SAPS assesses hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

MRI Protocol

The MRI examination used our previously published methods (Bartzokis et al, 2001; Bartzokis et al, 2009). Briefly, an initial coronal pilot sequence was used to align a sagittal MRI pilot sequence, which was then used to specify the position of the coronal image acquisition grid. The sagittal image containing the left hippocampus was used to define a

oblique coronal acquisition plane perpendicular to the hippocampus. Two consecutive coronal turbo sequences of the same brain slices were acquired. An inversion-recovery (IR) sequence (TR=2500, TI=625, TE=11, 1 repetition) and a transverse asymmetric dual spin-echo sequence with TR=2500, 2 repetitions, with an early echo TE=22 that produces the proton density (PD) image used in subsequent analyses (see below) and a late echo TE=90 image that is combined with the PD image to produce a calculated T₂ image used to delineate the brain/CSF border in subsequent analyses. Both IR and spin-echo sequences have 256 × 192 view matrix, 24 cm field of view, to produce co-registered 3 mm thick contiguous slices.

Image Analysis

All images were initially assessed and blindly rated for whether the protocol could be carried out adequately using both the IR and PD contrasts. The scans that qualified were analyzed in random order by a rater who was blinded to clinical and demographic characteristics of subjects. Details of image analysis are depicted in Figure 1. The ICM volume is calculated from three direct measures. Intra-rater reliability for these three measures was performed on a sample of nine healthy control subjects resulting in the following intraclass correlation coefficients: $r_{xx} = .92$ for white matter volume using the IR images, $r_{xx} = .95$ for white matter volume using the PD images, $r_{xx} = .99$ for intracranial volume.

Data analyses

It is known that age has a nonlinear (quadratic) relationship with white matter of healthy individuals over a wider age range (Bartzokis et al, 2001). Our current sample was restricted to individuals under 34 years of age, making a linear aging model appropriate for all the variables studied as the normal peaks are well above age 33. To standardize the change in ICM for the SZ group relative to normal controls, we used the HC group that was scanned with the patient cohorts. Normal age effects were estimated by regressing the variables of interest on age in the sample of HC subjects (N=12). The group mean was then subtracted from the respective raw scores of all subjects. Finally, the scores were divided by the within-study standard deviation, again calculated using the healthy controls. The procedure yielded standard scores in the healthy control samples with mean equal zero for all variables and standard deviation equal one (z-scores). We then evaluated differences between the schizophrenia patients with intramuscular or RLAI (N=9) versus oral risperidone or RisO (N=13) medication administration in separate analyses of covariance on the residual score of white matter ICM volume. The analysis used medication administration as the independent variable and controlled for race. In addition to comparing the medication administration groups, we also tested the group mean standardized scores for the combined SZ group against the normal controls, followed by contrasts of the RLAI and RisO groups separately against the normal controls. Chi-square analysis was performed to assess the effect of rated adherence to medication and treatment arm assignment on ICM. Finally, associations between change in ICM volume and measures of psychiatric symptom severity were assessed with Pearson correlational analyses.

RESULTS

Medication administration mode

The volumetric ICM change for each subject was the principal dependent variable of interest. When the two groups of SZ subjects are combined their standardized ICM change is significantly higher than the one for HCs (SZ: mean=0.75, sd=1.42; $t=2.48$, $df=21$, $p=.022$). The data for the individual treatment arms are depicted in Table 2 and Figure 2.

When the standardized ICM change/month was examined for each SZ group separately, in the RLAI group the minimal increase was .41 while in the RisO group, only 5 of 13 (38%) subjects had an ICM increase higher than .40 ($\chi^2=8.70$, $df=1$, $p=.003$).

Adherence

The patient's adherence to prescribed medication from baseline to endpoint was rated on a Likert scale with 1 being perfect adherence and 5 being the poorest adherence. The scores were further dichotomized into good adherence and poor adherence based on the median score (1.20) of the combined SZ group. Thus, <1.20 indicated good adherence while >1.20 was associated with poor adherence. Similarly, the volume change was also dichotomized into two groups based on a cutoff at the median volume change of $+.70$ for the combined SZ group. The chi-square was statistically significant ($\chi^2=4.55$, $df=1$, $p=.033$). The distribution is provided below in Table 3.

As expected, adherence and medication administration mode are highly confounded, as only one RLAI subject missed enough injections to have a lower than perfect adherence score of 1. Thus, when reassessing the data using the same ICM change cutoff and the RLAI versus RisO treatment assignment instead of the adherence score, the chi-square remained significant ($\chi^2=4.70$, $p=.030$).

For completeness, we examined the association between ICM volume change and two measures of psychiatric severity, the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for Assessment of Positive Symptoms (SAPS). The study participants were treated for approximately 6 months prior to randomization and they had achieved considerable symptom reduction at the time of baseline assessment; therefore, we did hypothesize that the brain volume and clinical symptom measures would be minimally related. As expected, given the limited sample size, the change in ICM volume was not significantly correlated with the change in SANS ($p>.18$) or SAPS ($p>.32$) global and subscale scores.

DISCUSSION

This prospective study extends our prior observation using cross sectional data (Bartzokis et al, 2009) and suggests that, early in the course of illness, antipsychotic medications may act, at least in part, by increasing ICM in SZ patients. In addition, the data suggest that medication delivery mode (LAI versus oral) may have a significant differential effect on ICM volume. During this six-month randomized controlled trial, RLAI promoted myelination and increased ICM significantly within this treatment group and tended to lead to greater increase than observed with RisO (Table 2 and Figure 2). Given that both treatment arms had the same active ingredient (risperidone), the data seem to support the suggestion that ICM may be sensitive to adherence or pharmacokinetic differences of oral versus LAI delivery and are consistent with the hypothesis that early in the SZ disease process, antipsychotic medications may help correct a deficit in the developmental trajectory of ICM (Bartzokis, 2012; Bartzokis et al, 2012).

The total antipsychotic exposure at the time of the baseline and end point assessments very likely influenced the ICM change we observed in SZ subjects. In a recent cross-sectional study of SZ (Bartzokis et al, 2012), we examined a wide range of durations of *oral* antipsychotic treatment (0–273 months) and observed that ICM was strongly affected by treatment duration. In that sample of SZ subjects, the ICM trajectory was significantly quadratic, reaching a peak after one year of oral antipsychotic treatment followed by a decline that was markedly accelerated compared to healthy subjects, whose ICM does not decline until after the fifth decade of life (Bartzokis et al, 2001; Bartzokis et al, 2012). In the

current study our assessment points spanned this peak in antipsychotic treatment-associated intracortical myelination (baseline assessment at 7.4 months of medication exposure with the follow up at 14.9 months). The minimal increase in ICM volume observed in the RisO group compared to the healthy controls (Table 2 and Figure 2) is therefore consistent with this trajectory of oral antipsychotic treatment that begins its decline after the first year of treatment. Furthermore, the significant increase in ICM volume observed with RLAI suggests that the trajectory observed for *oral* antipsychotic treatment may be modifiable with LAI treatment. In other words, LAI may be better able to maintain the higher ICM levels achieved during the early phases of antipsychotic treatment.

Supporting the possibility that antipsychotics initially increase ICM are observations that several polymorphisms of enzymes involved in dopaminergic transmission including dopamine metabolism through catechol-O-methyltransferase (COMT), dopamine-2 receptor, and Akt (also known as protein kinase B) are associated with glycogen synthase kinase-3 beta (GSK3 β) activation and increased risk for psychiatric diseases (Blasi et al, 2011) (reviewed in Bartzokis, 2012; Beaulieu and Gainetdinov, 2011). Activation of GSK3 β retards while *its inhibition promotes myelination* (Azim and Butt, 2011) (reviewed in Bartzokis, 2012). The long-standing hypothesis that SZ is associated with a *hyperdopaminergic* state predating the onset of psychosis (Howes et al, 2011; Seeman, 2010) is thus consistent with a dopamine-driven GSK3 β activation resulting in the myelination deficits observed in SZ (reviewed in Bartzokis, 2012). Dopamine-induced GSK3 β activation can be overcome by dopamine-2 receptor blockade, a property shared by all antipsychotics (Seeman, 2010). Early in treatment, antipsychotics have been shown to promote oligodendrocyte differentiation and myelin repair in rodent models (Chandran et al, 2012; Wang et al, 2010; Xu et al, 2010), increase cortical glial numbers in primates (Selemon et al, 1999), and increase intracortical myelin in humans (Bartzokis et al, 2009) (Figure 2). These initial promyelinating effects may contribute to the high levels of symptom remission that are especially striking within the first year of treatment (ranging from 70 to 87%) (Boter et al, 2009; Emsley et al, 2007; Lieberman et al, 1993; Nuechterlein et al, 2006; Robinson et al, 1999; Robinson et al, 2004; Saravanan et al, 2010).

The possibility that dopamine-2 receptor blockade promotes myelination is also supported by the results of the current study, which assessed a single compound (risperidone) delivered by two administration routes (LAI versus oral). The oral and LAI modes of delivery differ only in adherence and pharmacokinetics. These differences may be quite important because GSK3 β is an unusual serine/threonine kinase that is *constitutively active* and is primarily *controlled by inhibition*. *Consistent/continuous* inhibition of GSK3 β is much more likely with the LAI delivery. This could help explain why, although both RLAI and RisO increased ICM above healthy controls, RLAI increased mean ICM significantly and produced consistently larger ICM increases compared to RisO. This biologic effect on ICM may help explain important clinical correlates of RLAI treatment.

LAI delivery of typical antipsychotic medications has been available for several decades, however, an atypical LAI antipsychotic medication (RLAI), has only been available relatively recently. Treatment with RLAI has been associated with substantially improved clinical outcomes, decreased hospitalizations, and significant healthcare cost savings (Lindenmayer et al, 2009; Olivares et al, 2009b; Velligan et al, 2009; Willis et al, 2010) (reviewed in Keith, 2009). In a recent study, greater improvements in clinical parameters such as number and duration of hospitalizations were observed in RLAI-treated patients who were *recently* diagnosed with schizophrenia than for those with chronic schizophrenia (Olivares et al, 2009a) suggesting that advantages associated with LAI antipsychotic treatment might be particularly important early in the disease. However, these treatments remain underutilized, in part because of lack of clear biological evidence for benefits on

disease progression and concerns about metabolic side-effects (Lindenmayer et al, 2009) (reviewed in Keith, 2009). The current study suggests that the improved outcomes may be due, at least in part, to superior ability of RLAI to promote cortical myelination (Figure 2 and Table 3) and supports the hypothesis that a promyelinating effect may be a mechanism of action of antipsychotics (Bartzokis, 2002; Bartzokis et al, 2012) (reviewed in Bartzokis, 2012).

Strengths of this study include the use of imaging methods that target ICM (Figure 1), prospective design, and a young cohort of first-episode SZ subjects randomly assigned to the two treatment arms. The study also has several important limitations. The sample sizes of the treatment groups for the MRI study were small and not matched for race. This limitation was mitigated by the within-subject prospective design and statistically adjusting for the effects of race. The absence of SZ subjects matched for minimal pre-randomization antipsychotic exposure precluded assessment of very early medication-related changes in ICM and, although all subjects were placed on RisO for at least 10 weeks before randomization, treatment occurring prior to study entry was not standardized. The availability of only two time-points also limits our ability to define non-linear quadratic (inverted U) trajectories of change as suggested by our cross-sectional data (Bartzokis et al, 2012). To more fully define how LAI medications change the myelination trajectory beyond the first year of treatment, prospective randomized studies, over longer durations, and with multiple time points are needed.

The advent of *in vivo* neuroimaging methods that can dissect subtle differences in brain tissue characteristics may help clarify disease pathophysiology as well as the mechanisms of action of antipsychotic treatments. These methods can examine clinical endophenotypes as well as treatment response and thus improve targeting of treatment interventions. By modifying adherence and pharmacokinetics, RLAI may differentially impact myelination and account for the better long-term outcomes of RLAI compared to the oral treatments. Improved treatment decisions and early intervention may make it possible to increase effectiveness of antipsychotic treatments and thus provide an opportunity to mitigate the biologic and clinical trajectories of decline into chronic/refractory states of disease (Bartzokis et al, 2012; Lieberman, 2006).

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[ClinicalTrials.gov](https://clinicaltrials.gov) registration number NCT00330551 "Oral Versus Injectable Risperidone for Treating First-Episode Schizophrenia". K. Nuechterlein directs the schizophrenia research program that provided the diagnosis and randomized controlled trial treatment conditions for this study. G. Bartzokis and P.H. Lu had full access to all of the study data and take responsibility for the integrity of the data and the accuracy of data analysis.

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REFERENCES

- Alaerts M, Ceulemans S, Forero D, Moens LN, De Zutter S, Heyrman L, et al. Support for NRG1 as a susceptibility factor for schizophrenia in a northern Swedish isolated population. *Arch Gen Psychiatry*. 2009; 66:828–837. [PubMed: 19652122]
- Andreasen, NC. The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, IA: The University of Iowa; 1984a.

- Andreasen, NC. The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City: The University of Iowa; 1984b.
- Aston C, Jiang L, Sokolov BP. Microarray analysis of postmortem temporal cortex from patients with schizophrenia. *J Neurosci Res*. 2004; 77:858–866. [PubMed: 15334603]
- Azim K, Butt AM. GSK3beta negatively regulates oligodendrocyte differentiation and myelination in vivo. *Glia*. 2011; 59:540–553. [PubMed: 21319221]
- Bai YM, Ting Chen T, Chen JY, Chang WH, Wu B, Hung CH, et al. Equivalent switching dose from oral risperidone to risperidone long-acting injection: a 48-week randomized, prospective, single-blind pharmacokinetic study. *J Clin Psychiatry*. 2007; 68:1218–1225. [PubMed: 17854246]
- Barkovich AJ, Lyon G, Evrard P. Formation, maturation, and disorders of white matter. *AJNR. Am. J. Neuroradiol*. 1992; 13:447–461. [PubMed: 1566710]
- Bartzokis G. Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. *Neuropsychopharmacology*. 2002; 27:672–683. [PubMed: 12377404]
- Bartzokis G. Neuroglialpharmacology: white matter pathophysiology and psychiatric treatments. *Frontiers in Bioscience*. 2011; 16:2695–2733. [PubMed: 21622204]
- Bartzokis G. Neuroglialpharmacology: Myelination As A Shared Mechanism of Action of Psychotropic Treatments. *Neuropharmacology*. 2012; 62:2137–2153. [PubMed: 22306524]
- Bartzokis G, Altshuler L. Reduced intracortical myelination in schizophrenia. *Am J Psychiatry*. 2005; 162:1229–1230. [PubMed: 15930084]
- Bartzokis G, Altshuler LL. Biological Underpinnings of Treatment Resistance in Schizophrenia: An Hypothesis. *Psychopharmacol Bull*. 2003; 37:5–7. [PubMed: 15272475]
- Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-related changes in frontal and temporal lobe volumes in men: A magnetic resonance imaging study. *Arch Gen Psychiatry*. 2001; 58:461–465. [PubMed: 11343525]
- Bartzokis G, Lu PH, Amar CP, Raven EP, DeTore NR, Altshuler LL, et al. Long Acting Injection Versus Oral Risperidone in First-Episode Schizophrenia: Differential Impact on White Matter Myelination Trajectory. *Schizophrenia Research*. 2011; 132:35–41. [PubMed: 21767934]
- Bartzokis G, Lu PH, Nuechterlein KH, Gitlin M, Doi C, Edwards N, et al. Differential effects of typical and atypical antipsychotics on brain myelination in schizophrenia. *Schizophr Res*. 2007; 93:13–22. [PubMed: 17407804]
- Bartzokis G, Lu PH, Raven EP, Amar CP, DeTore NR, Altshuler LL, et al. Abnormal Trajectory of Intracortical Myelination in Schizophrenia Implicates White Matter in Pathophysiology and Antipsychotic Mechanism of Action. 2012 (*Submitted*).
- Bartzokis G, Lu PH, Stewart SB, Oluwadara B, Lucas AJ, Pantages J, et al. In vivo evidence of differential impact of typical and atypical antipsychotics on intracortical myelin in adults with schizophrenia. *Schizophr Res*. 2009; 113:322–331. [PubMed: 19616412]
- Bartzokis G, Nuechterlein KH, Lu PH, Gitlin M, Rogers S, Mintz J. Dysregulated brain development in adult men with schizophrenia: A magnetic resonance imaging study. *Biol Psychiatry*. 2003; 53:412–421. [PubMed: 12614994]
- Beasley CL, Honavar M, Everall IP, Cotter D. Two-dimensional assessment of cytoarchitecture in the superior temporal white matter in schizophrenia, major depressive disorder and bipolar disorder. *Schizophr Res*. 2009; 115:156–162. [PubMed: 19833481]
- Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev*. 2011; 63:182–217. [PubMed: 21303898]
- Blasi G, Napolitano F, Ursini G, Taurisano P, Romano R, Caforio G, et al. DRD2/AKT1 interaction on D2 c-AMP independent signaling, attentional processing, and response to olanzapine treatment in schizophrenia. *Proc Natl Acad Sci U S A*. 2011; 108:1158–1163. [PubMed: 21187413]
- Boter H, Peuskens J, Libiger J, Fleischhacker WW, Davidson M, Galderisi S, et al. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). *Schizophr Res*. 2009; 115:97–103. [PubMed: 19819114]
- Chambers JS, Perrone-Bizzozero NI. Altered myelination of the hippocampal formation in subjects with schizophrenia and bipolar disorder. *Neurochem Res*. 2004; 29:2293–2302. [PubMed: 15672553]

- Chandran P, Upadhyay J, Markosyan S, Lisowski A, Buck W, Chin CL, et al. Magnetic resonance imaging and histological evidence for the blockade of cuprizone-induced demyelination in C57BL/6 mice. *Neuroscience*. 2012; 202:446–453. [PubMed: 22119061]
- Cocchi L, Walterfang M, Testa R, Wood SJ, Seal ML, Suckling J, et al. Grey and white matter abnormalities are associated with impaired spatial working memory ability in first-episode schizophrenia. *Schizophr Res*. 2009; 115:163–172. [PubMed: 19837566]
- Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
- Emsley R, Rabinowitz J, Medori R. Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates. *Schizophr Res*. 2007; 89:129–139. [PubMed: 17095194]
- Flynn SW, Lang DJ, Mackay AL, Goghari V, Vavasour IM, Whittall KP, et al. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. *Mol Psychiatry*. 2003; 8:811–820. [PubMed: 12931208]
- Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *PNAS*. 2001; 98:4746–4751. [PubMed: 11296301]
- Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry*. 2003; 60:585–594. [PubMed: 12796222]
- Hof PR, Haroutunian V, Copland C, Davis KL, Buxbaum JD. Molecular and cellular evidence for an oligodendrocyte abnormality in schizophrenia. *Neurochem Res*. 2002; 27:1193–1200. [PubMed: 12462417]
- Hof PR, Haroutunian V, Friedrich VL Jr, Byne W, Buitron C, Perl DP, et al. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. *Biol Psychiatry*. 2003; 53:1075–1085. [PubMed: 12814859]
- Howes OD, Bose SK, Turkheimer F, Valli I, Egerton A, Valmaggia LR, et al. Dopamine Synthesis Capacity Before Onset of Psychosis: A Prospective [18F]-DOPA PET Imaging Study. *Am J Psychiatry*. 2011 [Epub ahead of print].
- Jaaro-Peled H, Hayashi-Takagi A, Seshadri S, Kamiya A, Brandon NJ, Sawa A. Neurodevelopmental mechanisms of schizophrenia: understanding disturbed postnatal brain maturation through neuregulin-1-ErbB4 and DISC1. *Trends Neurosci*. 2009; 32:485–495. [PubMed: 19712980]
- Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988; 45:789–796. [PubMed: 3046553]
- Katsel P, Davis KL, Haroutunian V. Variations in myelin and oligodendrocyte-related gene expression across multiple brain regions in schizophrenia: A gene ontology study. *Schizophr Res*. 2005; 79:157–173. [PubMed: 16139990]
- Keith S. Use of long-acting risperidone in psychiatric disorders: focus on efficacy, safety and cost-effectiveness. *Expert Rev Neurother*. 2009; 9:9–31. [PubMed: 19102665]
- Kemper, T. Neuroanatomical and neuropathological changes during aging and dementia. In: Albert, M.; Knoefel, J., editors. *Clinical Neurology of Aging*. 2nd ed.. New York: Oxford University Press; 1994. p. 3-67.
- Koenig SH. Cholesterol of myelin is the determinant of gray-white contrast in MRI of brain. *Magn Reson Med*. 1991; 20:285–291. [PubMed: 1775053]
- Le-Niculescu H, Balaraman Y, Patel S, Tan J, Sidhu K, Jerome RE, et al. Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B:129–158. [PubMed: 17266109]
- Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, et al. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry*. 2001a; 49:487–499. [PubMed: 11257234]
- Lieberman J, Jody D, Geisler S, Alvir J, Loebel A, Szymanski S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry*. 1993; 50:369–376. [PubMed: 8098203]

- Lieberman JA. Neurobiology and the natural history of schizophrenia. *J Clin Psychiatry*. 2006; 67:e14. [PubMed: 17107237]
- Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biol Psychiatry*. 2001b; 50:884–897. [PubMed: 11743943]
- Lindenmayer JP, Liu-Seifert H, Kulkarni PM, Kinon BJ, Stauffer V, Edwards SE, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *J Clin Psychiatry*. 2009; 70:990–996. [PubMed: 19497244]
- Martins-de-Souza D. Proteome and transcriptome analysis suggests oligodendrocyte dysfunction in schizophrenia. *J Psychiatr Res*. 2010; 44:149–156. [PubMed: 19699489]
- Nuechterlein KH, Dawson ME, Gitlin M, Ventura J, Goldstein MJ, Snyder KS, et al. Developmental Processes in Schizophrenic Disorders: longitudinal studies of vulnerability and stress. *Schizophr Bull*. 1992; 18:387–425. [PubMed: 1411329]
- Nuechterlein KH, Miklowitz DJ, Ventura J, Gitlin MJ, Stoddard M, Lukoff D. Classifying episodes in schizophrenia and bipolar disorder: criteria for relapse and remission applied to recent-onset samples. *Psychiatry Res*. 2006; 144:153–166. [PubMed: 17011635]
- Nuechterlein KH, Subotnik KL, Turner LR, Ventura J, Becker DR, Drake RE. Individual placement and support for individuals with recent-onset schizophrenia: integrating supported education and supported employment. *Psychiatr Rehabil J*. 2008; 31:340–349. [PubMed: 18407884]
- O'Brien JS, Sampson EL. Lipid composition of the normal human brain: gray matter, white matter, and myelin. *J Lipid Res*. 1965; 6:537–544. [PubMed: 5865382]
- Olivares JM, Peuskens J, Pecenak J, Ressler S, Jacobs A, Akhras KS. Clinical and resource-use outcomes of risperidone long-acting injection in recent and long-term diagnosed schizophrenia patients: results from a multinational electronic registry. *Curr Med Res Opin*. 2009a; 25:2197–2206. [PubMed: 19604073]
- Olivares JM, Rodriguez-Morales A, Diels J, Povey M, Jacobs A, Zhao Z, et al. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). *Eur Psychiatry*. 2009b; 24:287–296. [PubMed: 19195847]
- Parlapani E, Schmitt A, Erdmann A, Bernstein HG, Breunig B, Gruber O, et al. Association between myelin basic protein expression and left entorhinal cortex pre-alpha cell layer disorganization in schizophrenia. *Brain Res*. 2009; 1301:126–134. [PubMed: 19747901]
- Robinson DG, Woerner MG, Alvir JM, Geisler S, Koren A, Sheitman B, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 1999; 156:544–549. [PubMed: 10200732]
- Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004; 161:473–479. [PubMed: 14992973]
- Rouser G, Kritchevsky G, Yamamoto A, Baxter CF. Lipids in the nervous system of different species as a function of age: brain, spinal cord, peripheral nerve, purified whole cell preparations, and subcellular particulates: regulatory mechanisms and membrane structure. *Adv Lipid Res*. 1972; 10:261–360. [PubMed: 4344800]
- Saher G, Brugger B, Lappe-Siefke C, Mobius W, Tozawa R, Wehr MC, et al. High cholesterol level is essential for myelin membrane growth. *Nat Neurosci*. 2005; 8:468–475. [PubMed: 15793579]
- Saravanan B, Jacob KS, Johnson S, Prince M, Bhugra D, David AS. Outcome of first-episode schizophrenia in India: longitudinal study of effect of insight and psychopathology. *Br J Psychiatry*. 2010; 196:454–459. [PubMed: 20513855]
- Schmitt A, Steyskal C, Bernstein HG, Schneider-Axmann T, Parlapani E, Schaeffer EL, et al. Stereologic investigation of the posterior part of the hippocampus in schizophrenia. *Acta Neuropathol*. 2009; 117:395–407. [PubMed: 18777029]
- Seeman P. Dopamine D2 receptors as treatment targets in schizophrenia. *Clin Schizophr Relat Psychoses*. 2010; 4:56–73. [PubMed: 20643630]

- Selemon LD, Lidow MS, Goldman-Rakic PS. Increased volume and glial density in primate prefrontal cortex associated with chronic antipsychotic drug exposure. *Biol Psychiatry*. 1999; 46:161–172. [PubMed: 10418690]
- Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry*. 1995; 52:805–818. discussion 819–20. [PubMed: 7575100]
- Selemon LD, Rajkowska G, Goldman-Rakic PS. Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional, stereologic counting method. *J Comp Neurol*. 1998; 392:402–412. [PubMed: 9511926]
- Spencer KM, Nestor PG, Perlmuter R, Niznikiewicz MA, Klump MC, Frumin M, et al. Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci U S A*. 2004; 101:17288–17293. [PubMed: 15546988]
- Subotnik KL, Nuechterlein KH, Ventura J, Gitlin MJ, Marder SR, Mintz J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry*. 2011; 168:286–292. [PubMed: 21205805]
- Uranova NA, Vikhrevva OV, Rachmanova VI, Orlovskaya DD. Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: A postmortem morphometric study. *Schizophrenia Research and Treatment*. 2011; 2011
- Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res*. 2004; 67:269–275. [PubMed: 14984887]
- Valk J.; van der Knaap, MS. *Magnetic Resonance of Myelin, Myelination, and Myelin Disorders*. New York: Springer-Verlag; 1989.
- van der Knaap MS, Valk J. MR imaging of the various stages of normal myelination during the first year of life. *Neuroradiology*. 1990; 31:459–470. [PubMed: 2352626]
- Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry*. 2009; 70(Suppl 4):1–46. quiz 47–8. [PubMed: 19686636]
- Ventura J, Liberman RP, Green MF, Shaner A, Mintz J. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). *Psychiatry Res*. 1998; 79:163–173. [PubMed: 9705054]
- Vostrikov V, Uranova N. Age-related increase in the number of oligodendrocytes is dysregulated in schizophrenia and mood disorders. *Schizophrenia Research and Treatment*. 2011; 2011
- Vostrikov VM, Uranova NA, Orlovskaya DD. Deficit of perineuronal oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. *Schizophr Res*. 2007; 94:273–280. [PubMed: 17566708]
- Wang H, Xu H, Niu J, Mei F, Li X, Kong J, et al. Haloperidol activates quiescent oligodendroglia precursor cells in the adult mouse brain. *Schizophr Res*. 2010; 119:164–174. [PubMed: 20346631]
- Whitford TJ, Grieve SM, Farrow TF, Gomes L, Brennan J, Harris AW, et al. Volumetric white matter abnormalities in first-episode schizophrenia: a longitudinal, tensor-based morphometry study. *Am J Psychiatry*. 2007; 164:1082–1089. [PubMed: 17606660]
- Willis M, Svensson M, Lothgren M, Eriksson B, Berntsson A, Persson U. The impact on schizophrenia-related hospital utilization and costs of switching to long-acting risperidone injections in Sweden. *Eur J Health Econ*. 2010; 11:585–594. [PubMed: 20084535]
- Xu H, Yang HJ, McConomy B, Browning R, Li XM. Behavioral and neurobiological changes in C57BL/6 mouse exposed to cuprizone: effects of antipsychotics. *Front Behav Neurosci*. 2010; 4:8. [PubMed: 20305752]

Figure 1. In Vivo Measure of Intracortical Myelin (ICM) Volume of Frontal Lobe

The brain/CSF boundary in the frontal lobe was traced using the contrast of the calculated T2 image (not shown). The resultant brain ROI was pasted onto both the PD image (left panel) and IR image (right panel).

Left panel: Proton density (PD) image that is not sensitive to the cholesterol in myelin. White matter volume was measured using a histogram-based separation of the bimodal distribution of pixel intensities of white and gray matter (Bartzokis et al, 2007; Bartzokis et al, 2009). The gray matter histogram peak was eliminated using the shrink function to produce an ROI containing only white matter intensity pixels. The black line depicts the border between the gray and white matter. This same gray/white separation line is depicted on the IR image on the right as the gray line inside the white line.

Right panel: Inversion recovery (IR) Image of the same slice of brain as in the PD image on the left (both images obtained sequentially in the same imaging session). The IR image is optimal for detecting the high cholesterol in myelin and is used to obtain the “myelinated white matter volume” (using a histogram-based separation) that *includes* heavily myelinated parts of the deeper portions of gray matter. The white line shown in the figure separates myelinated and unmyelinated portions of gray matter. The PD and IR ROIs were manually corrected so that the only permitted difference was along the cortical white/gray matter boundary (Bartzokis et al, 2009). The difference between the white line (IR) and gray line (PD) ROIs is the measure of *intracortical* myelin (ICM). A contiguous three-slice volume centered on the anterior commissure was used for data quantification (Bartzokis et al, 2009). Volumes were computed by summing the cross-sectional area from each slice then multiplying by the slice thickness. Images from (Bartzokis et al, 2009), reprinted with permission.

Figure 2. Individual residual z-scores (based on healthy controls) of frontal lobe intracortical myelin (ICM) in first-episode schizophrenia subjects randomized to treatment with risperidone long-acting injection (RLAI) versus oral risperidone (RisO)

Both SZ groups have a positive mean z-score change and combined, they had a higher ICM than HCs ($t=2.48$, $df=21$, $p=.022$).

Within-Group t-test: ** $p = .005$

Between Group Test: RLAI versus RisO * $p = .093$.

Seven of thirteen RisO subjects had z-scores below the lowest value of the RLAI subjects as depicted by dotted horizontal line ($\chi^2 = 8.7$, $df=1$, $p=.003$)

[†]Results are based on covariance analyses adjusting for race.

Table 1

Characteristics of schizophrenia subjects matched in baseline medication exposure and randomized to a trial of long-acting injectable risperidone Consta (RLAI) versus oral risperidone (RisO)

	RLAI (n=9)	RisO (n=13)		
	Mean (SD)	Mean (SD)	t	p
Age, years	25.1 (4.9)	23.5 (4.6)	0.78	.45
Education, years	12.7 (2.0)	12.0 (0.8)	0.95	.37
Medication exposure prior to baseline scan (months)	8.5 (3.1)	6.6 (2.1)	1.75	.10
Age at psychosis onset, years	24.2 (5.0)	23.0 (4.5)	0.62	.54
Time between Scans, months	7.8 (1.7)	7.4 (1.2)	0.54	.59
	Male/female	Male/female	χ^2	p
Gender	7/2	9/4	0.20	.66

Residual z-scores (based on healthy controls) of frontal lobe intracortical myelin (ICM) in patients with first-episode schizophrenia randomized to treatment with risperidone long-acting injectable (RLAI) versus oral risperidone (RisO)

Table 2

		Baseline	Follow-up		Within-Group		Between-Group		
	MED	N	Mean (SD)	Change	t	p	F	p	d
Frontal ICM	RLAI	9	- .35 (1.26)	+1.53 (.98)	3.90	.005	3.13	.093	.81
	RisO	13	.07 (1.44)	+0.22 (1.60)	0.88	.39			

* Results represent change per month and based on covariance analyses adjusting for race.
d denotes effect size (Cohen's d) (Cohen, 1988).

Table 3

Relationship between adherence and ICM volume change

	Adherence	
Large ICM Increase	Good	Poor
Yes	8	3
No	3	8