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Dissecting the Heterogeneity of Treatment Response in First-Episode Schizophrenia

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The Mental Health Centers for Intervention Development and Applied Research (CIDAR) program prioritized research to provide an evidence base for biomarker development. At the Zucker Hillside Hospital (ZHH), our CIDAR grant supported research on a comprehensive investigation of treatment response and outcome in first episode schizophrenia. *Results* provide evidence that baseline neuroimaging, neurocognitive, and genetic measures are significantly associated with clinical response to treatment, and that our currently available interventions can effectively treat aspects of psychotic illness, as well as potentially reduce comorbidity associated with illness. Future research may include combining modalities to more robustly predict response and identify treatment targets, as well as to further develop more effective intervention strategies for these devastating and disabling disorders.

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In many areas of medicine, heterogeneity of patient outcomes is managed by the availability of multiple therapeutic options, and treatment decisions are guided by clinical biomarkers. Well-known examples in broad clinical use include the HER2 marker for herceptin treatment of breast cancer,[1] and natriuretic peptide levels for diagnosis and prognosis of heart failure.[2] By contrast, treatment options for patients with schizophrenia are relatively undifferentiated, and clinicians lack objective tools to dissect patient heterogeneity with respect to treatment and prognosis. Development of biomarkers in psychiatry can be critical to both the application of existing treatments and the development of novel treatments.

The announcement of the Mental Health Centers for Intervention Development and Applied Research (CIDAR) program in 2005 prioritized research to provide an evidence base for biomarker development. This announcement coincided with an important evolution in research at our institution, the Zucker Hillside Hospital (ZHH). Developments in neuroimaging, neurocognition, and molecular genetics provided the means to broaden our treatment research in first episode schizophrenia to encompass the development of individualized assessment tools to dissect the heterogeneity of treatment response in this important population. The CIDAR program provided the first NIH-funded mechanism to integrate these efforts into a comprehensive investigation of treatment response and outcome in first episode schizophrenia.

This theme is focused on the first episode of psychosis, which may be the most critical period in the life of an individual with schizophrenia, and remains the most opportune time for the study of key mechanisms that influence treatment response and outcome of this often chronically disabling disorder. Several factors render the first episode a critical research window: first episode patients are generally young, and therefore within a relatively restricted age range; they have a shorter duration of psychotic symptoms; and less illness-related functional and social impairment related to chronicity of illness. Perhaps most critical is that first episode patients have minimal prior psychopharmacological treatment, reducing medication confounds for research aimed at identifying the neurobiological substrates associated with illness and the prediction of illness course.

The ZHH CIDAR (P50MH080173; *Dissecting the heterogeneity of treatment response in first episode schizophrenia*; PI: Anil K. Malhotra), funded in 2008, integrated therapeutic knowledge and experience with the expertise of investigators utilizing neurocognitive, neuroimaging and molecular genetics approaches to biomarkers development. We focused on the assessment of a cohort of first episode schizophrenia patients participating in a 12-week clinical trial of 2 second generation antipsychotics (SGAs), aripiprazole and risperidone, and a follow-up extension phase of controlled treatment for

1 year. The primary CIDAR assessments were conducted prior to the initiation of treatment and during 12 weeks of double-blind treatment. The CIDAR comprises 3 cores supporting 3 independent projects, with additional NIH and FDA funding to support a supplemental project focused on the reactions of young people with early phase schizophrenia to tobacco smoking warning materials. The major aim of each of the 3 initial projects was to identify predictors of SGA response in this cohort, using neuroimaging, neurocognitive and genetic indices.

Progress to Date

At the conclusion of CIDAR patient recruitment in 2014, 198 first episode schizophrenia patients had entered the parent clinical trial, with a majority of them contributing additional data to the other projects within the CIDAR. Initial results include structural neuroimaging studies suggesting that observed antipsychotic-drug induced changes in fractional anisotropy, a putative measure of white matter integrity, may be related to changes in circulating lipid levels,[3] assessments of the relationship of cognitive function to brain connectivity,[4] and molecular genetics work identifying the melanocortin 4 receptor (MC4R) locus as a strong predictor of antipsychotic drug-induced weight gain.[5]

The CIDAR has been most successful in the adoption of resting state MRI (rs-fMRI) to identify biomarkers of antipsychotic drug response We have recently published a pair of studies demonstrating 2 facets of our approach to biomarker development in the context of CIDAR antipsychotic drug treatment: (1) identification of baseline predictors of treatment response and (2) identification of longitudinal indicators of target engagement.[6,7]

As an example of prognostic biomarker development, we utilized seed-based rs-fMRI analysis to examine the relationship between baseline (pretreatment) functional connectivity and subsequent response to SGA treatment. A striatal connectivity index (SCI) was established as a predictor of treatment response and replicated in a second sample.[6] Sensitivity and specificity in the replication sample suggests potential clinical application. Post-treatment rs-fMRI scans identified a different set of striatal connections that changed as a function of successful treatment.[7] These data are consistent with an independent study[8] in which symptom improvement with antipsychotic treatment was associated with changes in fronto-striatal connectivity. These fronto-striatal networks may serve as a measure of target engagement in the development of novel therapeutic agents.

In This Issue

In this theme issue of *Schizophrenia Bulletin*, we highlight results of the pivotal clinical trial at the heart of the CIDAR, as well as our most recent findings of prognostic relevance. Robinson and colleagues (this issue) present data from the first large scale double-masked first-episode randomized comparison of aripiprazole and risperidone. One hundred ninety-eight schizophrenia-spectrum participants (ages 15–40) were randomly assigned and followed for 12 weeks. Of note, positive symptom response rates did not significantly differ (62.8% vs 56.8%) between treatment groups nor was there a significant difference in the mean time to achieve clinical response. While positive symptom treatment efficacy was similar, there was substantial difference in side effect profiles. Patients treated with aripiprazole experienced greater akathisia during the trial, although differences were nonsignificant by the end of trial. By contrast, risperidone-treated patients had greater increases in total and LDL cholesterol, fasting glucose and prolactin levels. Taken together, the data suggest that while both drugs are effective in first episode patients, the metabolic advantages of aripiprazole may suggest it as a preferred choice over risperidone for young patients in whom treatment may be indicated for an extended period of time.

The second major aim of the CIDAR: to identify pretreatment neurocognitive indices that may be indicators of treatment response is addressed by Trampush and colleagues (this issue). Twelve weeks of treatment with aripiprazole and risperidone had minimal effects on cognitive function, as assessed with the MATRICS Consensus Cognitive Battery (MCCB). Although performance on indices of general cognitive function, working memory, and verbal learning improved over time, change was mediated by improvements in both positive and negative symptoms, reflecting "pseudospecificity" or practice effect.[9] These data are consistent with prior work from our group in first episode patients,[10] as well as studies in more chronic patients in which minimal effects of SGA treatment were found on neurocognitive function.[11] Intriguingly, however, at baseline, a measure of planning and reasoning significantly predicted whether positive symptom remission was achieved during the 12-week trial. These data suggest that a simple paper and pencil test may serve as a potentially useful predictive biomarker of antipsychotic drug response.

The third paper addresses genetic predictors of antipsychotic drug response. Previously, we have found that a polymorphism in the promoter region of the *DRD2* gene significantly influenced antipsychotic drug efficacy in first episode patients,[12] as well as in more chronically ill patients.[13] Moreover, the PGC consortium reported that a locus near the *DRD2* gene attained genome-wide significance for association to schizophrenia,[14] providing the first robust evidence that genetic variation in the dopamine system may influence illness susceptibility. Therefore, Zhang and colleagues (this issue) assessed the relationship of this new *DRD2* locus to treatment response and found evidence that variation at this risk locus was associated with positive symptom treatment response.

The final paper addresses whether tobacco warning materials designed to reduce cigarette smoking in the general population is effective in young patients with

schizophrenia. Schizophrenia is associated with intense smoking and related morbitiy and mortality. However, warning materials have not been specifically designed for use in this population. Coletti and colleagues (this issue) examined whether picture and video materials depicting the dangers of smoking, many of which can be quite graphic and potentially disturbing, would be acceptable to young patients with psychosis. Their data suggest that the materials were well-received with some evidence of a decline in smoking rates

Taken together, these papers as well as in our previous rs-fMRI publications, suggest that identification of biomarkers of antipsychotic drug response is feasible in first episode patient populations and that our currently available interventions can effectively treat aspects of psychotic illness, as well as potentially reduce comorbidity associated with illness. As our CIDAR-supported work found evidence that baseline neuroimaging, neurocognitive, and genetic measures are significantly associated with clinical response to treatment, the next steps will include combining modalities to more robustly predict response and identify treatment targets, as well as to further develop more effective intervention strategies that help ameliorate the suffering of patients with these devastating and disabling disorders.

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