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New Data Show Early Non-Response to Antipsychotic Treatment May Be Strong Predictor of Subsequent Non-Response for People with Schizophrenia

Findings indicate early non-responders unlikely to subsequently respond, have substantially more treatment costs, and may benefit from earlier change in treatment strategy

COLORADO SPRINGS, Colo., April 3, 2007 /PRNewswire-FirstCall via COMTEX News Network/ -- New data presented at the 2007 International Congress on Schizophrenia Research (ICOSR) suggest that antipsychotic drug response be assessed earlier than is presently thought, and challenge the current schizophrenia treatment paradigm for when to evaluate if an antipsychotic medication is working effectively.

The findings show that early non-response to antipsychotic medication, as early as two weeks into treatment, appears to strongly predict subsequent lack of response in patients with schizophrenia. Compared to "early responders" - patients who responded to their antipsychotic medication after two weeks of treatment - the "early non-responders" were less likely to achieve subsequent symptom remission, viewed medication adherence as less beneficial, had a lower level of functioning, and incurred twice as many total healthcare costs. The studies were conducted and funded by Eli Lilly and Company.

Early non-response may be a powerful marker to not only predict prognosis in schizophrenia, but also tailor appropriate treatment to the patient's immediate needs. These data support the need for clinicians' early evaluation of patients' treatment response, and the possible need for a change in the medication to potentially help minimize prolonging exposure to sub-optimal or ineffective treatment.

Current schizophrenia treatment guidelines recommend an initial trial of four to six weeks to determine if a patient will respond to an antipsychotic medication(i). However, these new data suggest this may be too long. Without early and effective treatment, patients with schizophrenia may experience devastating and costly events, such as hospitalization(ii), incarceration(iii), homelessness(iv), repeated relapses(v) and attempted suicide(vi). Current findings, which are based on post-hoc analyses, are consistent with independent research, suggesting drug effect seems to occur during the first two weeks of treatment(vii). However, additional research is still needed.

"These data are potentially very important in helping to establish the most cost-effective strategies for treating patients with schizophrenia," said Dr. John Kane, chairman of the department of psychiatry, neurology and neuroscience, The Zucker Hillside Hospital, Glen Oaks, New York and professor of psychiatry, Albert Einstein College of Medicine, Bronx, New York. "Furthermore, clinicians need better guidelines and predictors of treatment response in order to make informed treatment decisions. This is a further step in that direction."

Schizophrenia is a brain disorder characterized by acute episodes of delusions (false beliefs that cannot be corrected by reason) and hallucinations (usually in the form of "hearing" voices)(viii), known as positive symptoms(ix). Patients can also experience negative symptoms - such as diminished emotion, general lack of interest and depressive signs and symptoms - that are often more difficult to treat than positive symptoms(x). More than two million American adults have schizophrenia(xi), and more than 100,000 new cases are reported each year. The World Health Organization estimates the annual cost of schizophrenia at \$65 billion, including direct costs and lost productivity(xii).

"These data strongly advocate evaluating the potential benefit of antipsychotic medications earlier in treatment, so patients with schizophrenia can be spared from unnecessary increased exposure to a drug that is very unlikely to help them," said Dr. Cherri Miner, Lilly U.S. medical director, neuroscience. "Quick and effective symptom control is especially important for those patients with urgent needs and may increase the likelihood that patients will stay on their medication."

Key Findings

The first study, Predicting Response to Atypical Antipsychotics Based on Early Response in the Treatment of Schizophrenia, was a post-hoc analysis of data from five randomized, double-blind clinical trials comparing atypical antipsychotic medications in 1,077 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder, who were at least moderately ill at baseline and were treated for a minimum of two weeks. Patients were assigned into early responder or early non-responder groups at two weeks based on at least a 20 percent improvement on the Positive and Negative Syndrome Scale [PANSS] total score. (PANSS is the primary psychiatric scale used to measure change in schizophrenia symptoms.) Subsequent response at

endpoint was defined as at least a 20 percent improvement in PANSS total score (mild improvement), or at least a 40 percent improvement in PANSS total score (moderate improvement). The following was determined at the three-month endpoint:

- Seventy-four percent of patients identified as early responders or early non-responders maintained their status.
- Early responders showed significantly greater improvements in symptoms at all time points compared to early non-responders.
- Early non-response appears to be an accurate predictor of subsequent non-response to antipsychotic medications.

Researchers for the second study, Clinical, Functional, and Economic Ramifications of Early Non-Response to Antipsychotics in the Naturalistic Treatment of Schizophrenia, performed a post-hoc analysis on data from a one- year, multi-site, randomized open-label study of antipsychotic medications. Patients who completed eight weeks of treatment on their initial medication (n=443) were included in the analysis. Patients with early response were identified as having at least 20 percent improvement from study start - baseline - on PANSS total score after two weeks of treatment. Early responders were compared to early non-responders (patients that did not show at least a minimal level of early improvement) on symptom remission, physical and mental health functioning, perceptions of medication influence, and total healthcare costs at eight weeks. Statistically significant findings included:

- Early response or non-response at two weeks predicted subsequent response or non-response at eight weeks with a high overall level of accuracy (73 percent).
- Almost all (88.7 percent) of non-responders at eight weeks were correctly identified at two weeks (high specificity).
- Early non-responders were less likely to achieve symptom remission after eight weeks of treatment with the same antipsychotic (only 27.5 percent of early non-responders achieved remission vs. 46.9 percent of responders, $p<0.001$).
- Early non-responders improved less on physical and mental functioning ($p<0.05$), perceived adherence with medication as less beneficial ($p<0.05$), and incurred nearly twice as many total healthcare costs (\$4,336 vs. \$2,102, $p<0.01$).

These data need to be evaluated in the context of their limitations. These were post-hoc analyses limited to patients who completed eight weeks of treatment on the initially randomized medication. There is a need for additional research that measures a priori the predictive accuracy of early non-response as a reliable marker of subsequent non-response. There is also a need for additional studies that assess a priori the clinical, functional, and healthcare costs of early non-responders to antipsychotic medication regimens, and whether changes in the initial regimens result in subsequent improvements in treatment outcomes.

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