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Studies Show Schizophrenia Patients Taking Atypicals Stayed on Treatment Longer Than Patients Taking Older, Typical Antipsychotics

-- Longer time to all-cause medication discontinuation also leads to greater improvement in symptoms and quality of life for people with schizophrenia --

SAVANNAH, Ga., April 6, 2005 /PRNewswire-FirstCall via COMTEX/ -- Findings from three studies show that patients taking atypical antipsychotics stayed on their medication longer than older, typical antipsychotics when comparing time to all-cause medication discontinuation. The studies were presented this week at a major international psychiatric congress in Savannah, Ga.

One of the studies revealed that patients taking olanzapine or clozapine remained on treatment longer than other atypicals (risperidone, quetiapine, ziprasidone) or the typical perphenazine. Another study demonstrated that longer time to trial discontinuation appeared to be associated with significantly greater improvements in symptoms and quality of life as measured by standard psychiatric measures. Pearson partial correlations were used to assess the relationships between the length of time patients stayed in the trial and changes in symptoms [as measured by PANSS scores (Positive and Negative Syndrome Scale)] and health-related quality of life (e.g., Medical Outcomes Study 36-Item Short Form Health Survey, SF-36; Heinrichs-Carpenter Quality of Life Scale, QLS).

Schizophrenia is a severe and debilitating psychotic disorder often characterized by acute episodes of delusions (false beliefs that cannot be corrected by reason), hallucinations (usually in the form of non-existent voices) and long-term impairments such as diminished emotion, lack of interest and depressive signs and symptoms. In addition to psychiatric symptoms, patients with schizophrenia are at greater risk for medical comorbidities than the general population.

"When patients with schizophrenia stop taking antipsychotic medication as prescribed, they are at greater risk of relapse and hospitalization," said Jeff Swanson, Ph.D., associate professor of Psychiatry and Behavioral Sciences at Duke University Medical Center, and an investigator in one of the studies. "One study showed patients who adhered to recommended treatment consistently over time tend to experience reduction in symptoms, and improved functional outcomes. Other studies showed significant differences among antipsychotics with regard to patient adherence, which should be considered when choosing the most appropriate treatment for patients with schizophrenia."

Almost 60 percent of people with schizophrenia do not take their medications as prescribed by their physicians.(1) According to the American Psychiatric Association's guidelines for the treatment of schizophrenia, 60 to 70 percent of patients relapse within one year without maintenance treatment and almost 90 percent relapse within two years.(2)

In the treatment of schizophrenia, time to all-cause medication discontinuation is an index used to measure an interruption or cessation of antipsychotic treatment for any reason.

Key Findings

Time to All-Cause Discontinuation of Atypical versus Typical Antipsychotics in the Naturalistic Treatment of Schizophrenia

The Schizophrenia Care and Assessment Program (US-SCAP) is a 3-year non-randomized, multi-site, naturalistic study. US-SCAP is one of the largest naturalistic studies ever conducted in the United States. Using data from US-SCAP, time to all-cause discontinuation was evaluated from 1028 schizophrenia patients (1666 treatment episodes) taking antipsychotics. Of their 1666 treatment episodes, 1132 were with atypicals and 534 were with typical antipsychotics. Patients who were initiated on either atypical antipsychotics (olanzapine, clozapine, risperidone, quetiapine, ziprasidone) or typical antipsychotics (low, medium or high-potency) were compared on time to all-cause medication discontinuation.

"When we observed a highly diverse group of patients with schizophrenia undergoing treatment in real-world settings, we found that patients taking the atypical antipsychotics clozapine or olanzapine had a consistently and significantly longer time to medication discontinuation compared to patients treated with perphenazine and other typical antipsychotics," said Haya Ascher-Svanum, Ph.D., senior research scientist, U.S. Outcomes Research, Eli Lilly and Company. "The results were consistent across many diverse systems of care in both urban and rural environments regardless of gender, age and ethnicity."

When measuring time to all-cause discontinuation, atypical antipsychotics were found to have a lower discontinuation rate than typical antipsychotics, regardless of potency level. This was measured by the number of days of continuous treatment up to the first time medication was discontinued during the first year of treatment, provided the discontinuation was for more than 30 days.

- * When compared to perphenazine, a typical antipsychotic, only clozapine- and olanzapine-treated patients had a consistently and significantly longer time to medication discontinuation. The mean time to discontinuation differed by 84 days for clozapine and 48 days for olanzapine.

- * Clozapine, olanzapine, and risperidone had longer time to discontinuation versus haloperidol combined with prophylactic anticholinergic agents. The mean time to discontinuation was 64 days higher for risperidone, 87 days higher for olanzapine and 123 days for clozapine.

Given the scope of the study, there is potential bias due to non- randomization of treatment, which tends to reflect a patient's illness profile and physician's medication preferences.

Overall Treatment Effectiveness in Schizophrenia-Spectrum Disorders as

Measured by Time Continuing on Antipsychotic Therapy

In a retrospective integrated-analysis of 15 randomized, double-blind, head-to-head, published or presented clinical trials, researchers used weighted mean hazard ratios to determine the risk of discontinuation of other antipsychotics compared to olanzapine based on pooled data. The findings suggest that patients treated with olanzapine had a significantly greater likelihood of continuing treatment when compared to haloperidol, risperidone and ziprasidone. Olanzapine was also found to have greater treatment duration than quetiapine in a single study comparison. Kaplan-Meier estimators for probability of staying on treatment were obtained for each of the studies. The analysis was limited by the variable length of the studies, which ranged from 12 weeks to 104 weeks. All studies were from clinical, controlled trials, not naturalistic, open-label studies.

Among the findings, researchers concluded that when compared to olanzapine:

- * Patients treated with haloperidol had a 40 percent greater risk of discontinuing treatment.
- * Patients treated with risperidone had a 30 percent greater risk of discontinuing treatment.
- * Patients treated with ziprasidone had a 60 percent greater risk of discontinuing treatment.
- * Patients treated with quetiapine had a 40 percent greater risk of discontinuing treatment.

Longer Time to All-Cause Antipsychotic Discontinuation is Associated with

Better Schizophrenia Treatment Outcomes

A third study pooled data from six longer-term (greater than or equal to 24 weeks) double-blind, randomized studies assessed the impact of duration of treatment with patient outcomes. The analysis studied patients with schizophrenia taking olanzapine, haloperidol, risperidone, quetiapine, or ziprasidone. Longer participation in the trials was significantly associated with greater clinical improvements as measured by PANSS scores ($r=-0.42$ to -0.52 , $p < 0.001$), SF-36 component summaries and all subscales ($r=0.08$ to 0.28 , $p < 0.005$), and the QLS total and all subscales ($r=0.19$ to 0.31 , $p < 0.0001$). Pearson partial correlations were used to assess the relationships between the length of time patients stayed in the trials and changes in symptoms (Positive and Negative Syndrome Scale, PANSS) and health- related quality of life (Medical Outcomes Study 36-Item Short Form Health Survey, SF-36; Heinrichs-Carpenter Quality of Life Scale, QLS). Outcome measures were also compared between patients who completed their study and patients who did not. All of the trials were clinical controlled studies rather than naturalistic settings.

About Olanzapine

Olanzapine (Zyprexa(R), Eli Lilly and Company) is indicated for the treatment of schizophrenia, for acute bipolar mania, and for maintenance treatment in bipolar disorder.

The most common treatment-emergent adverse event associated with Zyprexa in placebo-controlled, short-term schizophrenia and bipolar mania trials was somnolence. Other common events were dizziness, weight gain, personality disorder (COSTART term for nonaggressive objectionable behavior), constipation, akathisia, postural hypotension, dry mouth, asthenia, dyspepsia,

increased appetite, and tremor.

The most common treatment-emergent adverse event associated with Zyprexa in combination with lithium or divalproex in 6-week combination bipolar mania trials was dry mouth. Other common events were weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, and paresthesia.

Hyperglycemia and diabetes mellitus -- Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including Zyprexa. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. All patients taking atypicals should be monitored for symptoms of hyperglycemia. Persons with diabetes who are started on atypicals should be monitored regularly for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Safety experience in elderly patients with dementia-related psychosis -- In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs. 1.5%, respectively). Risk factors that may predispose this patient population to increased mortality when treated with Zyprexa include age >80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g., pneumonia, with or without aspiration). Zyprexa is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia -- Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of Zyprexa in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with Zyprexa compared to patients treated with placebo. Zyprexa is not approved for the treatment of patients with dementia-related psychosis.

Prescribing should be consistent with the need to minimize the risk of neuroleptic malignant syndrome, tardive dyskinesia, seizures, and orthostatic hypotension.

Full prescribing information is available at www.zyprexa.com.

About Eli Lilly and Company

Lilly (NYSE: LLY), a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers -- through medicines and information -- for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com. P-LLY

LillyAnswers ensures that low-income Medicare enrollees with the greatest need have complete access to the Lilly products they require. The centerpiece of the patient assistance program, the LillyAnswers card, allows seniors and people with disabilities under Medicare to pay a flat \$12 fee for a 30-day supply of certain retail distributed Lilly drugs, including Zyprexa. Since Lilly implemented LillyAnswers in 2002, hundreds of thousands of people without prescription drug insurance have received more than a half million Lilly products. LillyAnswers enrollment applications are available by calling the toll-free number: 1-877-RX-LILLY (1-877-795-4559) or online at www.lillyanswers.com.

This press release contains forward-looking statements about the potential of Zyprexa for the treatment of schizophrenia and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that the product will continue to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

(1) Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, et al. "Adherence to Treatment With Antipsychotic Medication and Health Care Costs Among Medicaid Beneficiaries With Schizophrenia." *Am J Psychiatry* 2004 161: 692-699.

(2) Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J; American Psychiatric Association; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004 Feb;161(2 Suppl):1-56.

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SOURCE Eli Lilly and Company

Kerry Dixon of GCI Group, +1-212-537-8261; or Heather Lusk of Eli Lilly and Company,
+1-317-433-5600

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