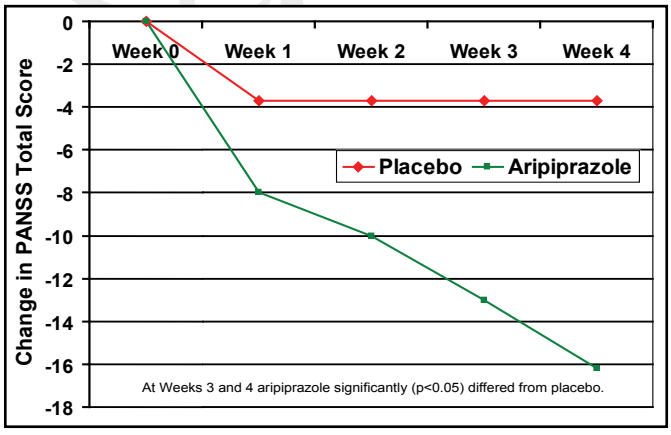
Pooled data from two 52-week efficacy studies that compared aripiprazole (20-30 mg/day) with haloperidol (7-10 mg/day) in patients with early (aged ≤40 years with first episode and duration of illness ≤60 months) schizophrenia [Crandall D et al. NR4-028] showed that significantly (p=0.001) more of the haloperidol (29%) patients discontinued treatment versus aripiprazole-treated patients (11%). Remission rates, defined by the Remission in Schizophrenia Working Group, were significantly higher with aripiprazole (38% vs 22%; p=0.003) and were achieved in a shorter time versus haloperidol.

In another study that compared aripiprazole treatment (mean 23.9 ± 6.4 mg/day) with placebo in patients with schizoaffective disorder, Glick ID et al. (NR4-039) reported fewer discontinuations with aripiprazole (42%) versus placebo (57%). PANSS total score was significantly (p<0.05) improved after 3-4 weeks of aripiprazole treatment versus placebo (Figure 1). Adverse events were similar and included anxiety, vomiting, dizziness, akathisia, tremor, and depression. Although EPS symptoms and metabolic values were similar, prolactin levels decreased more in the aripiprazole group (-5.6 vs -1.3; p<0.0001).

**Figure 1. Mean Change from Baseline to Endpoint in the PANSS Total Score.**



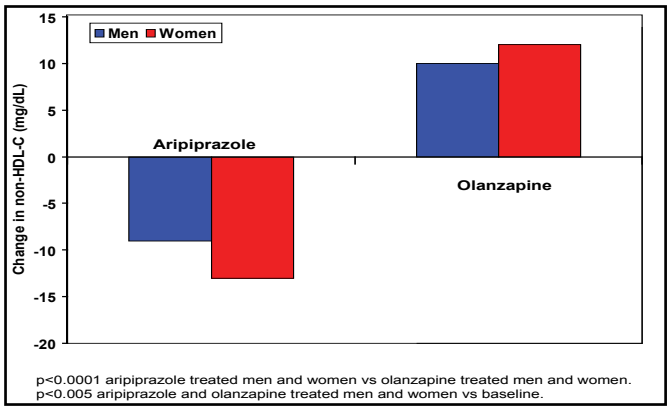

At Weeks 3 and 4, aripiprazole differed significantly (p<0.05) from placebo

In a pooled analysis of data from 5 studies, Kane JM et al. (NR4-097) noted significant decreases in PANSS total score after 4 weeks of treatment with aripiprazole (5-30 mg/day) versus placebo (-14.4 vs -2.4; p=0.001). The largest effect was noted for the hostility and uncooperativeness symptom domains.

In a further analysis of the above data and symptom domains, Janicak P et al. (NR4-080) reported that negative, positive, depression/anxiety, disorganized thought, and hostility domains significantly (p<0.05) improved after aripiprazole treatment versus placebo beginning at Week 2 in patients who were diagnosed as schizophrenic or having schizoaffective disorder.

Meyer JM et al. [NR4-053] noted that non-HDL cholesterol, a strong predictor of cardiovascular disease (often associated with schizophrenia treatment), significantly (p<0.001) decreased after aripiprazole treatment versus significant (p<0.001) increases after olanzapine treatment (Figure 2).

**Figure 2. Mean Change in Non-HDL at Week 26.**




In general, the investigators concluded that aripiprazole appears to be an effective first-line treatment for schizophrenia symptoms that has a favorable adverse event profile.

## Hippocampal Volume Predicts Conversion to Dementia in Patients with Mild Cognitive Impairment

In a study that had a 5-year follow-up, hippocampal volume (HV) was shown to be correlated with elevated risk in a cohort of elderly patients with mild cognitive impairment. Individuals who developed dementia had a smaller HV at baseline.

Patients with minimal cognitive impairment (MCI) as identified by the Clinical Dementia Rating scale (CDR) are known to have a conversion rate to dementia of 20%. The CDR Sum of Boxes score (CDR-SB; range 0-18) enables a quantitative evaluation of that impairment. To evaluate HV as a predictor of conversion, this study assessed 28 elderly patients who had a range of impairment at baseline. Impairment was gauged with the instruments of CDR-SB, MMSE (mini mental state examination), and ADAS-cog

(Alzheimer assessment scale). Based on these outcomes, patients were stratified as follows:

- CDR=0 (thus CDR-SB=0) = low risk
- CDR=0.5 and CDR-SB=0.5, 1, or 1.5 = medium risk
- CDR=0.5 and CDR-SB=2, 2.5, or 3 = high risk

Hippocampal volume was determined with a brain MRI within a maximum 4-month period after the initial neuropsychological evaluation. Scans were performed with a GE 1.5 Telsa scanner; imaging data were analyzed with Brains 2 software.

Results showed that HV was significantly smaller in high-risk individuals (0.21±0.014) as compared with individuals who were considered to be at low risk (0.28±0.033) or medium risk (0.26±0.037; $p<0.001$ for both). Those who went on to develop dementia two years before the final neuropsychological assessment had a smaller mean HV at baseline than those who did not ($p=0.02$); however, after receiver operating characteristic analysis was performed, no discrete HV value emerged as being useful to discriminate between the two groups. The HV correlated negatively with CDR-SB but did not correlate with age or years of education. The finding that individuals who developed dementia had smaller HV at baseline supports the theory that HV may be an important predictor of conversion.

## Treatment of Psychotic Depression with Combination Olanzapine/Sertraline

Results from the National Institute of Mental Health's Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) were presented at the American Psychiatric Association's 2008 Annual Meeting by Barnett Meyers, MD, Weill Medical College of Cornell University, New York, NY, on behalf of the collaborative study group. "There's a need for alternative treatments to ECT [electroconvulsive therapy]. One of the factors that I don't think is discussed enough is that there is a significant change in Hamilton scores following the ECT procedure – scores are found to have drifted upwards at the next assessment." There are also practical considerations, as ECT is not readily available on an out-patient basis.

To investigate the efficacy of a pharmacotherapeutic approach, STOP-PD looked at monotherapy with an antipsychotic versus an antipsychotic/antidepressant combination. In this 12-week, multicenter, placebo-controlled, double-blind trial, 259 patients with unipolar delusional depression were randomized to treatment with olanzapine/placebo or olanzapine/sertraline. Dosing regimens were initiated and then escalated as follows: olanzapine 5 mg, 10 mg, then 15 mg/day on Days 1, 4, and 7; with sertraline at 50 mg, 100 mg, and then 150 mg/day on the same schedule. Doses of 200 mg/day sertraline and 20 mg/day olanzapine were allowed for residual symptoms. Study endpoints included 2 weeks of Hamilton Rating Scale for Depression (HAM-D) 17 ≤ 10 ("remission") to demonstrate stability, and SADS delusional item measures of "no delusion" at the 2nd or both weeks of the depression remission period.

All patients in this study were aged 19 years and older, and 142 patients who were randomized were aged ≥60 years. All patients had HAM-D 17 scores of ≥21 at study entry. Patients with suicidal ideation were excluded.

After enrollment, subject discontinuations in this trial were high: 53% in the monotherapy arm and 37% in the combination arm. "The most common reason for both groups is the subject withdrawing consent," reported Meyers, "followed by clinical worsening." He added that insufficient response leading to discontinuation was higher in the monotherapy arm than for the combination: 10% versus 4.7%, respectively.

After 12 weeks, results showed a superior depression remission rate of 67% in the olanzapine/sertraline arm versus 41.9% for monotherapy ($p=0.036$). When broken down by age, both older (≥60) and younger patients had statistically superior results for the combination versus monotherapy ($p<0.02$), yet within the combination arm, results for the two age groups were not statistically different. "This did not support our hypothesis that younger patients would do better with the combination. In fact, numerically, older patients had a better response." SADS scores were reduced equivalently for both groups in both treatment arms.

The adverse events that were reported for this study did not differ significantly between the age groups, with the exception of more pedal edema seen in older patients and younger patients experiencing more weight gain. As expected, olanzapine-related weight gain was the most common adverse event overall (54.1%) and was dose-related.

When asked about weight gain concerns for patients being treated long-term, Meyers suggested that other atypical antipsychotics might be appropriate for use in this setting, cautioning, however, that little is known about the efficacy of these other atypical medications for psychotic depression or their adverse effects.