Cognitive effects of Olanzapine treatment in schizophrenia

As much as 85% of patients with schizophrenia have significant impairment in most domains of cognitive functioning. This impairment has been reported to be present shortly after recovery from the first period of psychosis and to persist. It is likely that it may precede the development of psychotic symptoms, becoming manifest, and contributing to the loss in function, during the prodromal period. The cognitive disturbance is slowly progressive in most patients, but a small proportion shows severe deterioration as the duration of illness increases. The degree of impairment in various domains of cognition differs in patients with schizophrenia, with some studies suggesting that the most severe cognitive impairments occur in measures of attention, verbal fluency, motor speed, and executive function. Moderate impairments in working memory, immediate memory span, and verbal learning and memory have been reported most frequently. All of these impairments are disproportionate to the mild intellectual decline demonstrated in patients with schizophrenia as a group.

In addition to the disease-related impairment in cognition in schizophrenia, there is considerable evidence that drugs with anticholinergic properties i.e. those used to prevent or to lessen extrapyramidal symptoms as well as some antipsychotics, can impair memory function. It has been suggested that the apparent improvement in cognition due to atypical antipsychotic drugs could be related to the lesser use of anticholinergic medications with these agents than is needed with typical neuroleptic drugs.

Olanzapine has been reported to have low-high antagonist affinities for all 5 muscarinic receptors and to be at least moderately anticholinergic. Consistent with this, clinical trials reported anticholinergic side effects and relatively high serum anticholinergic levels. However, subsequent studies report the contrary and suggest that its antimuscarinic activity was overestimated. Thus, there is a need to determine whether olanzapine has the effects on memory in man that would be expected of an anticholinergic agent.

Numerous studies report that novel antipsychotic agents improve cognitive function in patients with schizophrenia with small to moderate effect sizes. This is in contrast to typical antipsychotic medications. However, there are some studies that fail to find any differences between typical and atypical antipsychotic drugs on cognition. The improvement in cognitive function in schizophrenia has been suggested to be a better predictor of good outcome in social and work function than positive symptoms. Despite a number of cognitive evaluations of olanzapine, there is yet no consensus regarding the effects of olanzapine on cognition, and in particular, those cognitive areas that are sensitive to anticholinergics, such as memory.

This Institutional Review Board approved study reports on cognitive and clinical response to a 6-month open-label olanzapine treatment trial that was prospectively designed to study its effects on cognition in 34 patients who met DSM-III-R criteria for schizophrenia or schizoaffective disorder. Nine neurocognitive domains were assessed in two 2-hour sessions over 1 or 2 days. Patients were evaluated at baseline while receiving typical antipsychotic medications, following which they were switched to olanzapine treatment for a 6-month period (mean dose: 13,4 ± SD 7.8 (range 5-20) mg/day). Evaluations were repeated following 6 weeks and 6 months of treatment with olanzapine. Cognitive domains known to be sensitive to anticholinergic drugs, including visual, verbal, and working memory, were evaluated. The effect of olanzapine on cognitive domains believed to be important in functional outcome, including sustained attention, executive functioning, and psychomotor speed, were also evaluated.The BPRS was used to assess current clinical symptoms.

The mean age of the subjects was 41,4 years (standard deviation [SD] = 12,0 years), the mean age of illness onset was 24 years (SD = 6,5 years), the mean duration of psychiatric illness was 17,0 years (SD = 11,0 years), and the average education of the subjects was 12,9 years (SD = 2,8 years). Fourteen subjects with persistent positive symptoms despite 3 adequate trials with other antipsychotic drugs met criteria for neuroleptic resistance. Concomitant medication included lorazepam (4), sertraline (2), benztropine (2), and valproate (1).

Improvements in cognition after switching to olanzapine were noted across all domains of cognition, though not uniformly. Although performance was numerically the same or better on every cognitive test after switching to olanzapine, the improvement was significant in 12 of 19 cognitive tests. The BPRS Total score, and Positive Symptom subscale of the BPRS were significantly improved at the 6-week and 6-month follow-up. Seven of the 12 tests, including verbal learning and memory, Continuous Performance Test- Digit Prime, Stroop, Animal Naming, Controlled Word Oral Association Test, and Digit Symbol remained significant after controlling for positive symptoms. No significant effects were found on most measures of executive functioning. None of the cognitive measures showed a worsening after 6 weeks or 6 months of treatment. There was no evidence of an across-the-board improvement in performance between baseline and 6 weeks, or between 6 weeks and 6 months, which would suggest an overall practice effect. Regression analyses were conducted to determine significant predictors (age of subjects; sex; duration of illness; neuroleptic resistance) of cognitive improvement; however none of these measures significantly predicted cognitive response to olanzapine. The early termination sample (N = 24) was compared with the 6-month, prospective group (N = 10) and was not found to differ on any demographic, clinical, or cognitive measure.

The authors concluded that the 2 main hypotheses of the study were confirmed: olanzapine improved multiple cognitive domains, including those known to be important in functional outcome (attention; verbal fluency; selective attention; executive functioning; verbal and visual learning and memory; psychomotor tracking), and olanzapine did not impair measures sensitive to anticholinergic drugs (verbal and spatial memory). Further, that these findings supported that of an earlier study.

Reference

McGurk SR, Lee MA et al. Cognitive Effects of Olanzapine Treatment in Schizophrenia. Medscape General Medicine; MedGenMed Psychiatry and Mental Health, 2004.