P.2.e.004 Effect of initial ziprasidone dose on treatment of Korean patients with acute manic or mixed episodes

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Purpose: Although the optimal dose of ziprasidone in controlled clinical trial settings for schizophrenia has been well-documented, there is little evidence in support of the proper dose of ziprasidone in patients with bipolar disorder, especially when combined with a mood stabilizer. Moreover, East Asian patients receive relatively lower doses of antipsychotics than their Caucasian counterparts. We investigated the efficacy and tolerability of ziprasidone combined with divalproex to determine the relationship between the initial dose of ziprasidone and the treatment effect among Korean patients with acute bipolar manic or mixed disorders.

Method: This study was a 6-week, open-label, multi-center, flexible-dose prospective study involving combination ziprasidone and divalproex for the acute treatment of patients with bipolar manic or mixed episodes. The inclusion criteria included a current DMS-IV diagnosis of bipolar disorder with a current manic or mixed episode and a requirement for antipsychotic treatment on the basis of clinical experience or investigator preference. All patients were recruited during between May 2007 and December 2007 from 9 nationwide sites in Korea, including university-based hospitals or chronic mental institutions. The patients were categorized based on the initial dose of ziprasidone as follows: low (20–79 mg/day) and standard (80 mg/day). Ziprasidone was given in combination with divalproex in flexible doses, according to the clinical response and tolerability. The measures used to assess the efficacy of medication included the Young Mania Rating Scale (YMRS), the 17-item Hamilton Rating Scale for Depression (HAMD), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impression-Severity (CGI-S). The Extrapyramidal Symptom Rating Scale (ESRS) was administered at each visit in order to assess tolerability.

Result: Sixty-five subjects participated in this study. Forty-three patients (66.2%) were included in the low-dose start group and 22 patients (33.8%) were included in the standard-dose start group. In low-dose start group, most of patients started ziprasidone on 40 mg/day. There were no significant group differences in YMRS, CGI-S, BPRS, and HAMD total score changes based on repeated measure ANCOVA. However, the response and remission rates were significantly higher in the standard-dose group than the low-dose group. Based on logistic regression analyses, being on standard-dose start more than fourfold increased the odds of YMRS response (RR, 4.660; 95% CI, 1.097–19.792; $P = 0.037$) and remission (RR, 4.802; 95% CI, 1.326–17.395; $p = 0.017$) at the study endpoint. The combination of ziprasidone and divalproex was well-tolerated and adverse events were mostly mild. No statistically significant changes were recorded on the ESRS-behavior rating score, total score for Parkinsonism, total score for dystonia, total score for dyskinesia, CGI scale for Parkinsonism, and CGI scale for dyskinesia at the study endpoint compared to the baseline in both groups.

Discussion: Despite the many potential methodologic limitations of this open label study, the results of this multi-center, 6-week investigation showed that ziprasidone in combination with divalproex in the treatment of bipolar disorder with acute manic symptoms is safe and effective, especially when ziprasidone is initiated at the standard dose.

P.2.e.005 Korean medication algorithm for bipolar disorder

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Purpose: Since medical environment varies from country to country many countries have published their own treatment guidelines. In order to develop appropriate algorithms for treatment of bipolar disorder in Korea, medication algorithm project has been started in 2001, and Korean Medication Algorithm for Bipolar Disorder was published in 2002. In 2005, the revision of Korean Medication Algorithm for Bipolar Disorder was released. And then it was secondly revised in 2010. The aim of this study was to compare revised version of Korean Medication Algorithm for Bipolar Disorder 2010 with other recently published treatment algorithm and guidelines for bipolar disorder.

Methods: The authors reviewed the 4 recently published guidelines (The British Association for Psychopharmacology Guidelines for Treatment of Bipolar Disorder, Canadian Network for Mood and Anxiety Treatments Guidelines for the Management of Patients with Bipolar Disorder, National Institute for Health and Clinical Excellence Clinical Guideline for Bipolar Disorder, and The World Federation Society of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder) and treatment algorithms on the bipolar disorder to compare the similarities and discrepancies between Korean Medication Algorithm for Bipolar Disorder 2010 and the others.

Results: In aspects of treatment options, most treatment guidelines had some similarities. But there were notable discrepancies between the recommendations of other guidelines and those of Korean Medication Algorithm for Bipolar Disorder 2010 in which combination or adjunctive treatment were favored. Most guidelines advocated new atypical antipsychotics as first-line treatment option in nearly all phases of bipolar disorder. And most guidelines advocated lamotrigine in depressive phase and maintenance phase of bipolar disorder. Lithium and valproic acid were still commonly used as mood stabilizers in manic phase. And valproic acid was strongly recommended in mixed or psychotic mania. Mood stabilizers or atypical antipsychotics were selected

as first-line treatment option in maintenance treatment of bipolar disorder. As the more evidences were accumulated, more use of atypical antipsychotics such as quetiapine, aripiprazole and ziprasidone were prominent. For treatment of mania, Korean Medication Algorithm for Bipolar Diosrder 2010 suggested that the next step for inadequate response to the initial combination treatment with mood stabilizers and atypical antipsychotics was an addition of the other mood stabilizer. For bipolar depression, the next step was to add the other mood stabilizer or to add an atypical antipsychotics rather than to change to the other mood stabilizer. For the treatment of rapid-cycling bipolar disorder, Korean Medication Algorithm for Bipolar Disorder 2010 recommended the combination treatment of mood stabilizer and atypical antipsychotics, but other guidelines did not cover this issue independently.

Conclusions: This review suggests that the medication strategies of bipolar disorder have been reflected the recent studies and clinical experiences and the consultation of treatment guidelines may provide clinicians with useful information and a rationale for making sequential treatment decisions. It also has been consistently stressed that treatment algorithm or guidelines are not a substitute for clinical judgment; they may serve as a critical reference to complement of individual clinical judgment.

P.2.e.006 Assessment of the association between serum NGF and BDNF levels and hippocampus and amygdala volumes in adolescents with bipolar disorder

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Introduction: Bipolar disorder (BD) has been increasingly associated with abnormalities in neuroplasticity and cellular resilience in the brain regions involved in mood and affect regulation [1]. Brain Derived Neurotrophic Factor (BDNF) and Nerve growth factor (NGF) members of neurotrophin family and regulates neuroplasticity [2]. The amygdala, a region of specialized nuclei in the medial temporal lobe, is a critical component of the neurocircuity that regulates emotional valance. The hippocampus is one of the other key components of emotional regulatory networks in the brain [3].

Objective: The aim of the present study was to assess the correlation between hippocampal and amygdala volumes and serum NGF, BDNF levels in adolescents with BD in euthymic phase and healthy controls and to investigate associations between clinical variables such as duration of disorder and treatment and hippocampal and amygdala volumes and NGF, BDNF levels in patients with BD.

Method: Nineteen adolescents with BD and fourteen healthy adolescents aged between 13 and 19 were included in the study. Diagnoses were made according to DSM-IV. In the case and control group, history of seizures, history of pregnancy, severe head injury that causes loss of consciousness more than ten minutes, mental retardation ($IQ \leqslant 70$), the presence of a chronic medical disorder are the exclusion criteria. History of drugs and psychostimulant, antipsychotic or antidepressant use within three months before diagnosis, schizophrenia, pervasive developmental disorders were excluded in case group. All subjects underwent a blood sample collection between 09:00 am and 10:00 am, after an overnight fasting. After all patients gave their blood samples, they underwent to MRI scan within 24–72 hours.

The subjects were examined with a 1.5 T MR scanner (Intera, Philips, Netherland). Axial and coronal T1-weighted images of the whole brain were acquired using, 3-D Spoiled Gradient-recalled echo (SPGR) sequence. Blood samples and MRI data were acquired from patients when they were euthymic, Statistical analysis of the data was performed using SPSS 15 software. Comparison of the data between normal control subjects and subjects with BD was performed using Mann–Whitney U and Spearman correlation test and p-values <0.05 were considered significant.

Results: There was no significant difference between patients and controls in volume of either the right ($p = 0.790$) or left amygdala ($p = 0.920$), the right ($p = 0.362$) or left ($p = 0.920$) hippocampus or NGF ($p = 0.185$) or BDNF ($p = 0.389$) levels. In lithium medicated group, right hippocampal volumes were significantly larger than lithium unmedicated group ($p = 0.04$ mean+SD: 3358.3 ± 234.6) BDNF serum levels were significantly decreased in lithium medicated group ($p = 0.087$). The right hippocampal volumes were significantly smaller in valproate medicated group than valproate unmedicated group ($p = 0.018$, mean+SD: 2890.08 ± 155.3). There is a negative correlation between NGF serum levels and left hippocampal volumes in valproate medicated group ($r = -0.667$, $p = 0.050$).

Conclusions: According to our preliminary findings, both of valproate and lithium have different effects on brain structure in adolescents with BD during developmental period. This has revealed that future longitudinal follow-up studies need to sort out developmental and medication influences on brain structures over time in BD.

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P.2.e.007 Screening for bipolar disorder using a smartphone

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Purpose: The problems of misdiagnosis and underdiagnosis of bipolar spectrum disorders (BSD) have recently been highlighted. Studies of depressed patients have found evidence that BSD