

alter nuclear P-p65 levels in FC. These results suggest that olanzapine exerts some anti-inflammatory properties which may contribute to its therapeutic effects and/or toxicity.

## PS52

### Identifying common and distinctive epigenetic alterations between bipolar disorder and schizophrenia

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#### Abstract

**Introduction:** Gene-environmental interaction has been implicated in the pathogenesis of various mental disorders. Recent genome-wide association studies revealed that shared genetic polymorphisms underlie the pathogenesis of bipolar disorder (BD) and schizophrenia (SZ). Accumulating evidence suggests that epigenetic factors, which reflect the environmental insults and play a role in the regulation of long-lasting gene expression patterns, are involved in the pathophysiology of BD and SZ. However, it has not been fully studied whether epigenetic factors are shared or distinctive between BD and SZ. Recently, a large-scale methylome-wide association study (MWAS) was performed in peripheral blood of SZ. Here we performed pyrosequencing-based DNA methylation assays of the top five regions detected in the MWAS using peripheral blood of BD.

**Methods:** The sample consisted of peripheral blood of 448 BD patients and 458 healthy controls (CT) collected in Japan. We analyzed DNA methylation levels of the top five regions (FAM63B, ARHGAP26, CTAGE11P, TBC1D22A and intergenic region in chromosome 16 (ch16)), which showed hypomethylation in SZ, by pyrosequencing.

**Results:** Among the five regions, significant differences of DNA methylation level between BD and CT were detected in the three regions; FAM63B, TBC1D22A and intergenic region in ch16. Detailed analysis focusing on sex revealed the hypomethylation in intergenic region in ch16 in both male and female BD, and hypomethylation in FAM63B in male BD. On the other hand, we identified hypermethylation of the CpG sites in TBC1D22A in female BD.

**Discussion:** Hypomethylation of FAM63B, which is part of the networks regulated by microRNA that can be linked to neuronal differentiation and dopaminergic gene expression as well as intergenic region in chr16, may be common epigenetic alterations between SZ and BD. On the other hand, DNA methylation level of TBC1D22A may be linked to disease-dependent epigenetic alteration.

**Conclusion:** We identified common and distinctive epigenetic alterations between BD and SZ. These findings help to understand the pathophysiology of mental disorders and may contribute to develop the epigenetic-based biomarker using peripheral blood samples.

**Key Words:** schizophrenia, bipolar disorder, DNA methylation, epigenetic biomarker

## PS53

### Long term efficacy and tolerability of lamotrigine for patients with bipolar disorder; A retrospective study

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#### Abstract

**Objective:** Although lamotrigine has been widely used in bipolar disorders in many countries, in Japan, it was approved for bipolar disorders at July 2011. This study was conducted to investigate the long term efficacy and tolerability of lamotrigine.

**Method:** The subjects were 91 patients who were diagnosed as bipolar disorder (type1:n=40, type2:n=51) and treated with lamotrigine from Jan 2012 to Aug 2014 in our psychiatric hospital. We retrospectively investigated the clinical efficacy, safety and 52-week-continuation rate of lamotrigine, and also the relating clinical factors such as age, gender, diagnosis (type1 or 2), clinical state (depressive/manic/mixed), dose, concomitant psychotropic medication. We evaluated the efficacy as clinical global impression of improvement (CGI-I). Patients with a score of minimally (3), much (2) or very much improved (1) were considered as responders.

**Results:** Although the response rate of lamotrigine was 72.2 % for the patients with depressive and mixed state, The patients with type 2 bipolar disorders showed higher response rate than that with type 1 (78.4% vs 60.0%). Main side effect was skin rash (16.5 %). The total 52-week continuation rate was 58.1 %. The main cause of discontinuation was mucocutaneous symptoms at early phase (almost within 8 week) and following cause was lack of insight. The continuation rate in the patients with depressive and euthymic state was higher than those with mixed and manic state (66.2% vs 21.4%).

**Conclusion:** Lamotrigine was effective and well tolerable, especially for type 2 bipolar disorder. The management of the side effect as mucocutaneous symptoms and psychoeducation might be necessary to increase the long term continuation rate.

## PS54

### Effects of the potential lithium-mimetic, ebselen, on brain neurochemistry: A magnetic resonance spectroscopy study at 7 Tesla

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#### Abstract

**Introduction:** Lithium remains the most effective treatment for bipolar disorder but tolerance and safety issues complicate its clinical use. The antioxidant drug, ebselen, has been proposed as a possible lithium-mimetic based on its ability in animals to inhibit inositol monophosphatase (IMPase) and lower brain inositol, actions which it shares with lithium.

**Objectives:** The primary aim of the study was to determine whether treatment with ebselen lowered levels of inositol in the human brain. We also assessed the effect of ebselen treatment on other brain neurometabolites, including glutathione, glutamate, glutamine, and glutamate+glutamine (Glx)

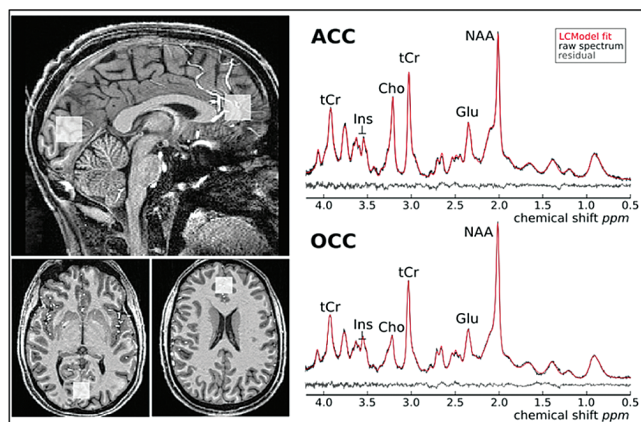


Fig. 1 : Voxel placement and representative spectra from the anterior cingulate cortex (ACC) and occipital cortex (OCC).

Table 1: Absolute metabolite concentrations ( $\mu\text{mol/g}$ ) given as mean  $\pm$  SEM, in anterior cingulate cortex (ACC) following treatment with ebselen (3600mg over 24 hours) or placebo

	Placebo	Ebselen	Significance - paired t-test
Inositol	$7.82 \pm 0.15$	$7.53 \pm 0.14$	0.028
NAA	$10.53 \pm 0.23$	$10.49 \pm 0.26$	0.789
GSH	$1.31 \pm 0.043$	$1.17 \pm 0.07$	0.033
GABA	$2.04 \pm 0.08$	$2.04 \pm 0.07$	0.984
Glutamate	$11.66 \pm 0.17$	$11.34 \pm 0.15$	0.010
Glutamine	$3.60 \pm 0.10$	$3.37 \pm 0.10$	0.024
Glx	$15.26 \pm 0.19$	$14.71 \pm 0.18$	0.001
Linewidth	$9.66 \pm 0.53$	$9.55 \pm 0.43$	0.743
SNR	$39.5 \pm 1.4$	$40.4 \pm 1.6$	0.264

**Methods:** We studied 20 healthy volunteers who were tested on two occasions receiving either ebselen (3600mg over 24 hours) or identical placebo in a double-blind, random-order, cross-over design. Two hours after the final dose of ebselen/placebo, participants underwent proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS) at 7 tesla (7T) with voxels placed in anterior cingulate and occipital cortex (Figure 1). Neurometabolite levels were calculated using an unsuppressed water signal as a reference and corrected for individual cerebrospinal fluid content in the voxel.

**Results:** Ebselen produced no effect on neurometabolite levels in the occipital cortex. In the anterior cingulate cortex, ebselen lowered concentrations of inositol as well as those of glutathione, glutamine, glutamate and Glx (Table 1).

**Conclusions:** The study suggests that at the dosage used, ebselen produces a functional inhibition of IMPase in the human brain. The ability of ebselen to lower indices of glutamate activity are consistent with its action, reported in animal experimental work, to inhibit the enzyme, glutaminase. Ebselen appears to have potential as a repurposed treatment for bipolar disorder and it would be of interest to see if similar biochemical alterations are produced by ebselen treatment in this patient group.

## PS55

### Parkinsonism induced by valproic acid: a case report and review of literature

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#### Abstract

Valproic acid (VPA) is a drug commonly used as an antiepileptic and mood stabilizer. We describe a patient who presented with particularly severe, but reversible parkinsonism during VPA treatment. We also provide a literature review on VPA-induced parkinsonism. The case was a 75-year-old woman who was diagnosed with bipolar disorder and was stabilized on lithium since the age of 50. At the age of 74, she started complaining of freezing of gait, which did not improve with L-DOPA administration. She became depressed and was admitted to a psychiatric ward. The patient complained of finger tremors, which improved after lithium was switched to 1000-mg/day VPA. The

change in medication ameliorated both the tremors and the depressive symptoms. She was discharged from the hospital after 2 months. However, her parkinsonism worsened 4 months after discharge. The subsequent exacerbation of parkinsonism left her bedridden and unable to walk by herself. Her Unified Parkinson's Disease Rating Scale score was 98. Because drug-induced parkinsonism was suspected, VPA was gradually withdrawn thereafter. Forty-five days later, she was able to walk by herself with a cane. The Unified Parkinson's Disease Rating Scale score improved to 11. Improvement of parkinsonism after withdrawal of the medication led us to diagnose her as age-related vascular parkinsonism exacerbated by medication. Previous studies showed that approximately 20% of patients on chronic VPA therapy developed tremor (Aleksandar J et al., 2006). In majority of the previously reported VPA-induced parkinsonism cases, the parkinsonism was improved after discontinuation of the drug (Mahmoud F et al., 2011). Although drug-induced parkinsonism is a frequent side-effect of VPA, severe cases such as the present case are uncommon. The recognition of VPA-induced parkinsonism is of great clinical significance, because appropriate treatment results in significant improvement of symptoms.

## PS56

### A smaller percentage of unipolar depression patients with manic or hypomanic switch during acute antidepressant treatment convert to bipolar disorder

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#### Abstract

**Objective:** To investigate 3-year outcomes of unipolar depression patients with manic or hypomanic switch during acute antidepressant treatment.

**Methods:** A review of medical records revealed 37 consecutive patients admitted from 1997 to 2002 who underwent an antidepressant-induced manic or hypomanic switch fulfilling DSM-IV criteria. Their clinical courses were retrospectively investigated after discharge.

**Results:** Of the 37 patients, 29 (78.4%) were followed for 3 year after discharge. None developed a manic episode, while 10 developed a hypomanic episode, including 2 patient who were lost after emerging from a hypomanic episode during the observation