The Role of Lamotrigine in the Treatment of Bipolar Depression

Anatolii Tsarkov1, 2 & Petro Petlovanyi2
1Chainama Hills College Hospital, Lusaka, Zambia
2Department of Psychiatry, School of Medicine, University of Zambia, Lusaka, Zambia

Abstract: Mood disorders are the most common psychiatric disorders. According to epidemiological studies, the prevalence of unipolar depression among the general population is 2-7%, while the risk of this disorder during life is 5-17%1, 2. The total prevalence of Bipolar Spectrum Disorders is 0.5-1.5%, and the chance of occurrence during life is about 5%1, 3. The choice of a rational and appropriate treatment is essential. This article describes the principles of pharmacotherapy of Bipolar Disorder, particularly bipolar depression. The role of anticonvulsants as drugs of choice in the treatment of this disorder is described in details. Special attention is paid to the effectiveness of lamotrigine.

Keywords: Lamotrigine, Bipolar Depression, Anticonvulsants.

Introduction

The problem of Bipolar Disorder (BD) is one of the leading in psychiatric practice. Sufficient and adequate method of treatment of BD depending on the type and phase of the disorder, the severity of mood and comorbid somatic (medical) pathologies is crucial. The consequences of the depressive phase are more significant than the manic phase. The total duration of depressive episodes is three times higher than that manic, so it is given special significance.

The principles of pharmacotherapy of unipolar and bipolar depressions differ significantly. The treatment strategy for unipolar depression includes a strategy toward the patient's exit from the depressive state and prevention of its subsequent relapse. Instead, in bipolar depression, the main goals of therapy are interruption of the phasic of the process and prevention of the development of the subsequent phase of the disorder. That is why, standard therapy with "classical" antidepressants in most cases of episodes is insufficient, because it leads to an increased risk of phase inversion.

In addition, it is aimed at eliminating manifestations of depressive symptoms, but not eliminating the mechanisms of development of the disorder. To achieve this effect, use of other class of drugs, such as mood stabilizers, should be considered. However, in the United States, more than a half of the patients with bipolar depression continue to receive traditional antidepressant therapy, which does not have the best effect on treatment outcomes and prognosis4. In this regard, an adequate and effective pharmacotherapy of BD is one of the most urgent tasks of modern psychopharmacology.

Drugs of choice for the treatment of Bipolar Disorder

Antidepressants are not considered as drugs of choice in the treatment of BD, especially the depressive phase, due to the high risk of phase inversion, although they are often prescribed as an adjunct therapy if the poor effectiveness of previous therapy, the severity of the condition, or the presence of severe suicidal tendencies4. Antipsychotics may be helpful in a management of depressive episode with psychotic features or in manic phase. However, the drugs of choice in BD therapy for any phase (depression or mania) are mood stabilizers.

The first mood stabilizer, which opened a fundamentally new stage in the pharmacotherapy and who is among the most popular representatives of this group is lithium. The use of lithium is associated with the ability to influence both depressive and manic symptoms, and also to prevent the inversion of phases. At the same time, the effectiveness of lithium in the therapy of the depressive phase is significantly lower to its effectiveness in the treatment of mania. In addition, lithium has certain disadvantages: a slow development of the clinical response (especially in the depressive phase), insufficient effectiveness in the case of BD with a rapid alternation of episodes and mixed states, the presence of significant side effects, the need to monitor serum concentrations of the drug, which is not always achievable in clinical practice. Therefore, mood stabilizers from a group of anticonvulsants, both the first and the new generation, have been widely used in clinical practice.
Nowadays, anticonvulsants are considered as a leading component of BD therapy at any phase and it is recommended by all global clinical recommendations. They affect the manifestations of both mania and depression, have a preventative effect on the inversion of phases, and also have efficacy in long-term maintenance therapy.

The effectiveness of anticonvulsants in the treatment of BD is determined by their pathogenic effect on the processes of neuroplasticity in the brain and according to modern concepts, play an important role in the development of this disorder, as well as their neurotrophic properties.

In BD, morphological and neurochemical changes are revealed in the central nervous system, which are similar, on the one hand, to recurrent depression, and on the other hand to neurodegenerative diseases. These are decrease in the volume of individual regions of the cortex, hippocampus, basal ganglia and the number of interneuronal connections, atrophy of apical dendrites of pyramidal neurons, hyperactivation of potential-dependent Na+ and Ca2+ ion channels, decrease in the amount of the main neurotrophic factors - BDNF and Bcl-2 proteins, NMDA receptors, etc.

All the main anticonvulsants used as mood stabilizers, namely carbamazepine, valproate and lamotrigine, affect all of the above mechanisms. They increase in the density of interneuronal contacts in the regions of the brain, contribute to increase the concentration of the main neurotrophic brain factors, improve receptor-effector reactions (activation of adenylyl cyclase and protein kinase), and suppress excessive activation of ion channels of neuronal membranes.

The clinical effects of these drugs and the scope of their use in BD are significantly different. This indicates the presence of unidentified relationships between the points of application of anticonvulsants at the molecular level and their effect on manic and depressive symptoms in this disorder. The establishment of these relationships will further optimize the pharmacotherapy of BD.

Lamotrigine for treatment of Bipolar Depression

One of the most promising drug in pharmacotherapy of BD, which opened a new stage in the treatment is lamotrigine. Lamotrigine was originally proposed as an antiepileptic agent. The mechanism of its action is determined by the blockade of potential-dependent slowly inactivating sodium channels of neurons, as a result of which the ejection into the synaptic membrane of excitatory amino acids, primarily glutamate. It is important to note that this effect is manifested only in neurons with the presence of epileptogenic activity and is not observed in the normal functioning of neurons. Lamotrigine acts primarily as a corrector of synaptic glutamatergic neurotransmission, a kind of "normalizer" of glutamatergic neurons. In addition, lamotrigine also blocks potential-dependent calcium channels of the hippocampal neurons, although the physiological role and detailed mechanisms of this phenomenon are not yet fully understood. As a result of this effect, the pathological hyperactivity of the hippocampal neurons in the CA1-region is reduced, which is largely responsible for the regulation of the emotional sphere, cognitive functions and subcortical-cortical relationships.

Subsequent studies have revealed the presence of a number of other pharmacological effects of lamotrigine. Certain extents are able to explain the effect of this drug in BD. These are non-selective inhibition of reuptake of monoamines (including serotonin), blockade of monoamine oxidase (MAO) A and B, multidirectional effects on glucose metabolism and cerebral blood flow in various regions of the central nervous system (mainly in the paralimbic region, thalamus and cortex) and increase GABA level in the brain. Finally, in the recent years, these beneficial effects of lamotrigine on neuroplasticity and receptor-effector reactions in the CNS have also been identified. In general, all of the above makes it possible to assert that lamotrigine has a very diverse, polytypic effect on the main links in the pathogenesis of BD.

Lamotrigine is considered not only as the most promising medication for pharmacotherapy of BD, but also as the only real tool for correcting clinical symptoms without concomitant destabilization of the emotional sphere. The available results of numerous clinical trials convincingly testify the prospects and uniqueness of lamotrigine in BD treatment, which makes it possible to characterize this drug as a mood stabilizer with antidepressant properties.

The evidence base for lamotrigine efficacy in the monotherapy of a depressive episode within any type of BD was obtained during randomized, double-blind, placebo-controlled trials. It found a dose-dependent effect of lamotrigine, which develops fairly quickly (during the first three weeks of administration). The effectiveness of treatment exceeds 50%. The most important advantage of lamotrigine in comparison with antidepressants is the absence of inversion affect.
The preventive effect of lamotrigine on the development of an episode of any type of BD should be noted. It is especially important to distinguish the positive effect of this drug in BD with frequent phase changes. This clinical form is the most difficult for pharmacotherapy when the use of antidepressants, lithium or carbamazepine were ineffective. In the course of a long-term study of the effects of lamotrigine in bipolar depression, the remission period extended to the entire time of patient observation - up to 1 year.

Thereby, lamotrigine effectively eliminates the cyclicity of mood changes in the emotional sphere, which forms the clinical basis of this form of disorder. In addition, the efficacy of lamotrigine has been described when used in combination with lithium for the purpose of further prophylaxis of manic development. The efficacy of lamotrigine was determined by using various scales: The Hamilton Rating Scale for Depression (HAM-D), The Clinical Global Impression – Improvement scale (CGI-I), The Montgomery–Asberg Depression Rating Scale (MADRS), etc. In addition, this drug has a beneficial effect on the concomitant cognitive impairment in these patients.

In the comparative trials of the efficacy of lamotrigine and other anticonvulsant drugs in the treatment of BD, higher efficacy rates of lamotrigine were found in comparison with valproate, gabapentin and topiramate. The researchers noted the absence of negative dynamics of body weight that is often associated with the use of valproate, and a negative effect on the cognitive functions that in some cases observed in the therapy with topiramate.

Effective doses of lamotrigine in the treatment of bipolar depression, established during clinical trials, are 200–400 mg / day. They should be achieved by titrating the initial dose (25-50 mg / day), depending on the availability of concomitant therapy, for six weeks. When a maintenance stabilizing dose of 200-400 mg / day is reached, it is possible to cancel the additional treatment and switch to monotherapy with lamotrigine.

The most important advantages of lamotrigine in the treatment of BD are its good tolerability and a relatively small number of side effects associated with using the drug, among which most often were skin rashes (2-10%), headache, dizziness, accommodation disorders and dyspeptic disorders. In most cases, the described reactions did not require the withdrawal of treatment. Nevertheless, it is possible to develop (1: 800 - 1: 1000) fairly severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) both in isolation and within the manifestations of the general hypersensitivity syndrome to the drug. In this case, lamotrigine should be immediately withdrawn.

It should be emphasized that the incidence of side effects (especially skin rash) depends directly on compliance with the dose titration regime and the characteristics of combined therapy. Despite the fact that lamotrigine in general does not have a clinically significant potential for drug-to-drug interaction, it should be remembered that its biotransformation is slowed down when administered together with inhibitors of hepatic enzymes (in particular, with valproates) and acceleration with inductors of these enzymes (in particular, carbamazepine, phenytoin and phenobarbital). Pharmacokinetic interaction with lithium combination was not revealed.

Conclusions

It should be noted that anticonvulsants are the most important component of a complex pharmacological treatment of BD, and subsequent studies of their mechanisms of action and clinical effects, as well as specific application in different clinical types of the disorder course will contribute to further success in clinical psychopharmacology and psychopharmacotherapy. Lamotrigine is considered as a drug of choice in the treatment of bipolar depression. The variety of dosage forms of lamotrigine provides an opportunity to rationally choose the strategy of pharmacotherapy depending on the type of BD, the polarity of the phase, the severity of the clinical symptoms, concomitant therapy, etc. Consequently, all of the above determines the effectiveness of therapy and prognosis, positioning lamotrigine as the drug of choice in the treatment of BD, especially depressive episode.

References


