

# Polypharmacy in bipolar disorder: Present status and future perspectives

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## Abstract

Polypharmacy in the treatment of bipolar disorder is the rule rather than the exception. This has been documented in numerous studies carried out in many countries. Some studies indicate that polypharmacy may be more effective than monotherapy in the prophylaxis of BD. Considering the complex neurobiological basis of BD and the ever-better-known mechanisms of action of mood stabilizers (MS) and second-generation antipsychotics (SGA), one can suppose that in the future the neurobiological signature will allow for the administration of drugs that will cover all disturbed underlying processes. This review presents data showing that individualized approach to the prophylactic treatment of bipolar patients based on their specific neurobiological profile and better knowledge on the effects of the use of two or more mood stabilizing drugs may significantly improve the efficacy of the treatment.

## Introduction

Bipolar disorder (BD) is a severe and relatively common mental disorder. Disability, cognitive and functional impairment, as well as excess in mortality, particularly by suicide, are common sequelae of this disease [1]. Early hypotheses linked pathogenesis of BD with disturbances of monoamine systems and genes involved in the metabolism of neurotransmitters and receptors [2]. In recent years several new hypotheses regarding the neurobiology of BD have been formulated namely: mitochondrial dysfunction and energy metabolism, oxidative stress, up-regulation of glutamatergic neurotransmission and disturbances in the immuno-inflammatory system [3-5]. Numerous studies using magnetic resonance imaging, have documented structural changes in the brain in patients with BD [6,7].

The first agents that have been shown to be effective in the acute treatment of bipolar episodes and in prophylactic treatment were lithium, valproates and carbamazepine. These properties caused these drugs to be called mood stabilizers (MS) [8-10]. A few decades later mood stabilizing effects of second-generation antipsychotics (SGA) (aripiprazole, olanzapine, risperidone, quetiapine, asenapine, and ziprasidone) as well the new generation of antiepileptic drugs (lamotrigine) have been documented. This led to a significant progress the pharmacological treatment of BD.

The mechanism of action of MS is still yet to be clarified. Lithium affects signal transduction, through its inhibition of second messenger enzymes such as inositol monophosphatase (right), by modulation of G proteins (middle). Valproates and carbamazepine have, inter alia, a regulatory effect on voltage-gated Na<sup>+</sup> channels [11]. Other data suggest a positive impact of lithium on neurogenesis, brain remodeling, angiogenesis, mesenchymal stem cells functioning, and inflammation. This influence is mediated by the inhibition of the glycogen synthase kinase-3, a serine/threonine kinase [12]. The growing evidence point that lamotrigine, lithium and valproate have also anti-inflammatory effect but it differs in details [13,14].

The mechanism of action of SGA is related to their agonistic on 5-HT<sub>2A/2C</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub> and modulation of D<sub>2</sub> receptors as well as on the regulation of glutamatergic System impact [15]. More recent studies have shown that these medications have a more profound effect on brain biochemistry. The stimulation of 5-HT<sub>1A</sub> receptors, the blockade of 5-HT<sub>2</sub> receptors and the stimulation of TrkB receptors by brain-derived neurotrophic factor (BDNF) may increase Ser9 phosphorylation of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) finally causing neuroprotective and neurogenic effects [16].

The risk of recurrence in bipolar disease is high, therefore the selection of appropriate medications for prophylaxis of relapse is a crucial and sometimes difficult therapeutic decision. Lithium, the oldest mood stabilizing agent but it is still considered the most effective in this class [17]. For that reason, is recommended as first-line monotherapy for the relapse prevention [18]. However, it is fully effective only in one-third of bipolar patients whereas in others the prophylactic effect is not satisfactory [19]. The clinical efficacy of other medications is also limited to prevention of mainly manic (olanzapine, risperidone-long acting injection, and valproate) or depressive episodes (lamotrigine) [18]. Interestingly, all medications recommended for treatment of BD except lithium were originally developed for the treatment of schizophrenia or epilepsy. It can, therefore, be assumed that the postulated mechanism of their action probably does not precisely cover the underlying neurobiology and pathophysiology of BD.

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The gap between available and “ideal” medications causes that the practice of using two drugs is often encountered. One of the many definitions of polypharmacy states that this is the long-term use of two or more psychiatric medications in the same patient and the other that it refers to use of two or more medication of the same class to treat the same condition [20]. The practice of the simultaneous use of two or more drugs, to treat one disease is common in medicine and arterial hypertension and epilepsy can be examples.

### How often is polypharmacy used in BD?

Results of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study conducted between 1998–2005 showed that patients, who achieved a remission of symptoms were prescribed averagely 2.05 medications. Lithium (37.1%) Valproate (34.4%) and atypical antipsychotics (33.2%) were the most commonly prescribed medications [21]. Moreover, this study showed that 40% of subjects used 3 or more drugs, while 18% received 4 or more agents [22]. The analysis of medical records of bipolar I patients admitted at Butler Hospital in Providence, during the 2010 calendar year found that patients took an average of 3.31 (SD = 1.46) psychotropic medications at the time of hospitalization. Moreover, 36% reported taking complex polypharmacy defined as concomitant use of  $\geq 4$  psychotropic medications [23]. Data from a large European multicenter study (AMSP) showed that from 1994 to 2009, 85% of all BP patients received more than one class of psychotropic medications [24]. A more recent report demonstrated that 69% of BP patients were treated with antipsychotics (AP) and 30.4% of them received AP polypharmacy. Furthermore 85.5% of those who were on AP polypharmacy also received MS and/or antidepressant. In turn, 76.9% of bipolar patients who were on one AP, received concomitant treatment with MS and/or antidepressant [25]. A significant increase of use of SGA was observed between 1998 (18%) and 2009 (49%) in the United States. Inversely, in the same period the proportion of patients treated with MS decreased from 82% to 67% [26]. During a 2-year Australian prospective, non-interventional, observational study of 239 outpatients with the diagnosis of bipolar I or schizoaffective disorder participants took a median of 5 different psychotropic medications. The application of polypharmacy was associated with some improvement in clinical and functional outcomes [27]. Results of these studies confirm that polypharmacy is used in the majority of bipolar patients.

Treatment guidelines published in recent years recommend monotherapy, preferably with lithium, and augmentation with valproates or SGA if lithium is ineffective [6,14-17]. Except for patients with rapid cycling BD where complex treatment is recommended [19,28-31].

### Is polypharmacy more effective than monotherapy in the prophylactic treatment of bipolar patients?

Results of randomized, placebo-controlled trials suggest that the combination of mood stabilizer and SGA seems more effective than monotherapy in the treatment of acute mania in comparison to monotherapy [32,33].

We have the increasing number of evidence indicating that that polypharmacy may be more effective than monotherapy in the prophylactic treatment of BD. The Balance study demonstrated that during 2-years follow up, combination therapy with lithium plus valproate more effectively prevents relapses in BP I patients than monotherapy with valproates but not lithium [34]. However, in the conclusions the authors state that the results of this study could neither confirm nor refute a benefit of combination therapy compared with lithium monotherapy.

Results of the naturalistic, prospective study conducted by Peselow. *et al.* [35] showed that patients diagnosed with BP I after acute manic episode were more likely to remain in remission during the two-year follow-up when they took two or more drugs in comparison to those who were on monotherapy. In another study of BP I patients followed for one year after hospitalization due to a manic episode, a combination of atypical antipsychotic and mood stabilizers appeared to be more effective in comparison to monotherapy with mood stabilizers in preventing rehospitalization [36].

A recently published meta-analysis of 15 randomized clinical trials confirmed that participants who received prophylactic treatment with the combination of mood stabilizer and SGA experienced fewer recurrences than those on monotherapy. In contrast to other SGA, only adjunctive treatment with quetiapine reduced both manic and depressive relapses [37].

### The future of polypharmacy in BD

The aim of the interesting recent study was to assess the effects of the combination of lithium, valproate, quetiapine and lamotrigine on markers of inflammation, bioenergetics mitochondrial function and reactive oxygen species in the culture of neuron-like and lipopolysaccharide-stimulated C8-B4 cells [38]. The researchers have shown that quetiapine alone has a proinflammatory effect, but in combination with lamotrigine, both drugs have the anti-inflammatory effects. Moreover, results of this study suggest that various combinations of these drugs have a regulatory effect on mitochondrial capacity. Also, Leu, *et al.* [39] found the evidence that due to a different effect of lithium and valproate on inflammatory mechanisms these MS prescribed in polypharmacy may provide a complementary immunomodulatory effect. These data may suggest that the use of two drugs may cause new qualitative effects.

The recent Danish study has given a hope that the assessment of multisystem composite biomarkers including expression levels of 19 candidate genes in peripheral blood, plasma levels of BDNF, NT-3, IL-6 and IL-18, leukocyte counts, and urinary markers of oxidative damage to DNA and RNA may be useful in diagnosing of BP [40]. Moreover, few studies showed that neuroimaging data might also be useful in differential diagnosis of bipolar patients but also in the selection of proper treatment [41,42]. The specific combinations of these biomarkers measured on several biological levels may suggest a new neurobiological basis of affective disorders which clinically may manifest as different psychopathological dimensions and finally these “neurobiological signatures” can be helpful in developing algorithms for choosing the individualized treatment [43].

Therefore, further clinical studies of neurobiological and clinical correlates of treatment response are needed to formulate more detailed recommendations to improve the effective management of BD.

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