



## EVALUATION OF THE MOOD-STABILIZERS ASSOCIATED NEUROCOGNITIVE EFFECTS IN BIPOLAR PATIENTS

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**Abstract.** Cognitive impairments in domains like attention, verbal memory, verbal learning and executive function are now considered a feature of bipolar disorder, due to their persistence during the remission periods. Beside that fact, in bipolar patients there are cognitive dysfunctions induced by mood-stabilizers, which are the first line drugs used in this specific pathology. The evaluation of memory and attention functioning, motor speed reaction, associative productivity and creativity represents a necessary step for the monitoring of bipolar patient, because of the anticonvulsants impact over these cognitive variables. The functional prognosis, bipolar patient ability to cope with professional and social duties, as well as his quality of life depend, in a significant proportion, upon monitoring symptoms and decreasing the factors associated with a negative impact on cognitive functions.

**Keywords:** mood-stabilizers, bipolar disorder, cognitive dysfunctions, side effects, memory, attention

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### Cognitive deficits in bipolar disorder - overview

Neuropsychological studies conducted in bipolar patients showed the existence of dysfunctions in many areas of information processing, including emotional adequacy, memory and attention maintenance. Both bipolar disorder *per se* and mood-stabilizers may be responsible for the occurrence of these cognitive dysfunctions. During manic, depressive and mixed episodes, patients with bipolar disorder have significant cognitive dysfunction, as reflected in the neurocognitive tasks performances [1,2]. Some neurocognitive deficits are not completely resolved during periods of euthymia, e.g. reduction of attention, memory and executive functions, a phenomenon that creates difficulties in patients' socio-professional reintegration, while adversely affecting the functional outcome and quality of life.

This persistence of cognitive deficits during euthymia suggests the possibility of a bipolar disorder feature, characterized by attentional deficits, verbal

learning difficulties, verbal memory and decision making impairments.

A clinical trial compared cognitive performance in (1) patients with bipolar depression treated with lithium or valproic acid, (2) bipolar depression untreated patients and (3) healthy subjects [3]. This study concluded that there are deficits in emotional processing and attention maintenance in patients receiving treatment compared with untreated subjects. A naturalistic study which compared the neurocognitive effects of 5 mood-stabilizers [4], included 159 bipolar patients who received different antiepileptic drugs or lithium, monitored through a battery of neurocognitive screening tests. Lamotrigine and oxcarbazepine neurotoxicity was the lowest, while topiramate, valproate and carbamazepine have been associated with an increased negative effect on neurocognition, and lithium effect was intermediate between the two.

### Main effects of mood-stabilizers on cognition

Lithium is involved in determination of the cognitive dysfunction's degree in bipolar patients, even if changes were relatively modest, reversible and occur only in some areas of cognitive performance. Isolated observations indicate that lithium may decrease creativity, by reducing productivity and the emergence of associations idiosyncrasies in euthymic bipolar patients, but this phenomenon is

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reversible after cessation of the therapy [5,6].

Thus, a study investigated the effects of lithium therapy discontinuation and „hidden“ restart (after a single-blind methodology) on creativity, cognition and global movement performance, in 46 patients that received maintenance treatment. In these euthymic patients lithium showed that performances of memory, motor speed and associations productivity improved during the period when patients did not receive the drug [5]. These effects were more clearly observed in younger patients with less severe depressive episodes in their personal history and who had higher lithium serum concentrations.

The second study evaluated the effect of lithium carbonate on productivity and idiosyncratic written associations, occurring in euthymic outpatients, diagnosed with bipolar disorder [6]. This research included 22 subjects, assessed weekly during treatment with lithium, then during two weeks of placebo and then for another two weeks after resuming therapy with active substance. It was noted that discontinuation of lithium treatment significantly increased associative productivity and idiosyncratic associations, and reintroduction of lithium reversed these effects. Thus, the authors concluded that lithium affects the normal function of neurological circuits involved in generating verbal associations and creativity.

A quantitative analysis of the literature [7] on the cognitive side effects of lithium in patients with bipolar disorder identified 4 studies that met methodological quality criteria and showed a negative effect of lithium on memory and information processing speed, often without subjective complaints or insight in these changes. The authors argue that a correct analysis needs to assess the plasma levels of lithium and thyroid hormones levels and to quantify the degree of emotional disturbance in bipolar patients in the presence of these neurocognitive changes. If all those variables remain within normal range and cognitive deficits persist, it is advisable, however, to reduce the dose of lithium or to use another, slow-release, lithium formula.

There are also studies in healthy volunteers, which do not support the existence of semantic creativity and aesthetic perception measures after two weeks of lithium, although a decrease of the motor speed was observed [8]. A study of 3 weeks showed that treatment with lithium (mean dose 1569 mg/day) does not impair attention or implicit memory retrieval but has lightweight deleterious effects on learning [9].

In patients treated with lithium, the following issues have been observed: reduced verbal memory performance, such as loss of ability to recover information from the long or short memory [5,10] and reducing the motor speed [11,12]. Euthymic

bipolar patients receiving lithium monotherapy have working memory deficits that may correlate with executive dysfunction in the frontal structures [13]. Evaluation by fRMN of these patients, carrying out two tasks involving working memory, compared with a control group, showed the existence of decreased bilateral activation of frontal, temporal and parietal areas and increased activation of precentral gyrus and left medio-frontal lobe.

Retrieval and motor deficits observed during therapy with lithium remitted in bipolar patients after stopping treatment [5]. There are also situations where the dosage reduction has been reported to diminish cognitive side effects. Adding triiodothyronine may represent a viable strategy to reduce cognitive complaints associated with lithium therapy [14].

An analysis of longitudinal evaluations in patients treated with lithium [15], which included studies published between 1968-2000, showed the following effects in the cognitive area: psychomotor slowing, decreased performance on tests of verbal memory, no dysfunction on tests of constructional visuospatial ability, lack of attention or concentration capacity, deterioration and lack of a cumulative negative effect. There are also studies that did not detect clear effects of lithium on cognition [16-18]. Subjective reports of deficits in memory retrieval during lithium therapy were associated with severity of depression [19] or therapeutic noncompliance [20], although objective memory deficits have been reported in euthymic bipolar patients treated with lithium [21].

**Anticonvulsants** such as carbamazepine, valproate or topiramate were associated with improvements in neurocognitive adverse events if patients were switched from lithium therapy. Thus, for example, when switching from lithium to sodium valproate there were observed reductions in cognitive, creative and motivational deficits in a series of seven clinical cases [22].

**Topiramate** is associated with an increased risk of cognitive adverse effects [23]. In clinical trials for the treatment of migraine and epilepsy common adverse effects were observed at doses up to 400 mg/day, including psychomotor retardation, impaired retrieval, difficulties in words finding, drowsiness and fatigue [24]. In healthy adults, doses of 333 mg/day topiramate, administered for 12 weeks, were associated with decreased cognitive performance up to two standard deviations in a significant number of neurocognitive scales [25]. In patients with epilepsy, the introduction of topiramate, in addition to previous antiepileptic treatment, was associated with significant decreases in verbal fluency, attention and concentration, processing speed, communication skills, working

memory and perception [26]. Discontinuation of therapy with topiramate in patients with epilepsy was accompanied by improvements of attention, verbal fluency, verbal working memory and short-term spatial memory [27]. Some studies show that the severity of cognitive dysfunction associated with topiramate decreases when a constant dose has been reached, but other studies refute this observation [28,29].

Topiramate acts at pharmacodynamic level by increasing GABA-mediated inhibition, modulation of calcium channels and blocking non-NMDA mediated excitotoxicity. The mechanism through which topiramate would produce cognitive dysfunction is not clearly established.

**Lamotrigine** was associated with difficulties in concentration in 2% of patients vs. 1% placebo and confusional states have been reported in at least 1% of bipolar patients receiving the drug to prevent relapses for periods up to 18 months [24]. Cognitive problems associated with administration of lamotrigine appear relatively infrequently and are typically transient. There are studies showing no negative effect on neurocognitive functioning in bipolar patients, even with the possibility of a beneficial effect on immediate memory and verbal fluency [30]. After 8-16 weeks of treatment with lamotrigine in an open-label trial, for a manic episode or bipolar depression, overall improvements were seen in cognitive functioning compared to baseline (memory, attention, reasoning) [31].

Evaluation by post-hoc analysis of data from a prospective, open label trial which investigated the effectiveness of lamotrigine in 1175 patients, age over 13 years, diagnosed with bipolar disorder type I, showed after 12 weeks improvements in a scale of self-cognition (Medical Outcomes Study Cognitive Scale, MOS-Cog), which correlated significantly with depressive and manic symptoms reduction ( $p < 0.0001$ ) [32]. Patients who were receiving lamotrigine and antipsychotics had a lower degree of cognitive improvement than those who were on mood-stabilizer monotherapy ( $p = 0.0039$ ).

**Sodium valproate** has been associated with mild memory and attentional dose-dependent impairments, reductions in verbal memory and increased decision time, without accompanying visual and spatial processing alterations [21,23,33]. Valproate-induced cognitive effects are reversible after drug discontinuation. The comparison of (1) 17 bipolar euthymic outpatients treated with lithium, (2) 11 euthymic outpatients, with the same diagnosis, who were receiving valproate and (3) 29 control subjects showed that immediate memory was affected similarly in both groups actively treated, which suggest an intrinsic deficit of bipolar disorder or a common substrate of lithium and valproate influences on

immediate verbal memory [21].

A clinical study included 10 healthy volunteers, male, who received consecutively, for two weeks, sodium valproate and placebo [34]. Valproate doses were increased to 1000 mg/day during the second week of treatment. Significant differences between the two groups were observed in very few areas of investigation (reaction speed reduction, slowing of decision-making processes), but they have supported the hypothesis of cognitive dysfunction induced by valproate.

**Oxcarbazepine** does not appear to adversely affect long-term memory in healthy volunteers. A two-weeks study, which included administration of 300-600 mg/day oxcarbazepine to 12 healthy volunteers was associated with improved motor speed and attentional performance compared to the baseline level, as well as with increased subjective sensation of vigilance and speed of associations [35]. In another study, administration of higher doses (oxcarbazepine 1200 mg/day) to 10 healthy volunteers during eight days led to a decline in motor speed from the baseline, less pronounced than during carbamazepine treatment [36].

**Carbamazepine** administered to patients with epilepsy can cause subtle learning deficits, while in healthy volunteers a prolongation of stimulus evaluation time was observed [23]. Carbamazepine induces mild changes in memory during visual evoked potential trials, but was not associated with a significant negative effect on motor speed [23].

**Levetiracetam**, evaluated in preclinical studies, is not associated with adverse effects on cognition, and trials involving patients with epilepsy show a relatively favorable neurocognitive profile, at least in comparison with topiramate [37,38]. Levetiracetam may even improve attention in patients with epilepsy, as some four months duration trials have reflected [38].

**Gabapentin** has been proved to be effective in open studies with bipolar depression, but results from controlled studies were conflicting. Cognitive effects of gabapentin, lamotrigine and topiramate in healthy volunteers were compared in a randomized, single-blind, parallel-group trial [39]. Neurobehavioral assessments were performed at baseline, 3 hours, 2 and 4 weeks after drug administration. Patients who received topiramate (2.8 mg/kg) had significantly weaker performance than those who received gabapentin (17 mg/kg) or lamotrigine (3.5 mg/kg) on verbal fluency tasks and visual attention. Doubling the anticonvulsant concentration led, after 2 and 4 weeks, to topiramate association with significant deficits in verbal memory and psychomotor slowing compared with baseline, while patients who received gabapentin and lamotrigine did not show this association.

Another randomized, double-blind study compared the cognitive effects of gabapentin and carbamazepine [40] in healthy elderly volunteers, showing that both anticonvulsants could induce mild cognitive adverse effects, without significant differences between the two groups.

## Conclusions

Although many mood-stabilizers determined only mild or moderate cognitive problems in patients with bipolar disorder, assessing the impact of medication on cognitive functioning is an area of interest for clinical research, both in terms of finding solutions to reduce the current dysfunction associated with pharmacological agents and to stimulate the discovery of new mood-stabilizers without such negative effects. It is important to slowly titrate the dose of anticonvulsants in order to reduce the drugs' negative impact on cognition and performance, and to switch patients from lithium to another mood-stabilizer, whenever significant cognitive difficulties appear.

The most important cognitive dysfunctions associated with mood-stabilizers are: (1) associations fluency decrease, memory and verbal learning impairments, lower motor performance when lithium is administered, but lithium neurocognitive adverse effects are reversible; (2) minor learning deficits, memory and reaction time slowing when valproate and carbamazepine are administered; (3) bradykinesia, retrieval and attentional disturbances, difficulty finding words during topiramate therapy. Oxcarbazepine and lamotrigine have a favorable neurocognitive profile, and gabapentin needs further studies. Another important aspect is the psychotropics related cognitive dysfunctions differentiation from a clinical perspective, like retrieval impairments, psychomotor and attentional deficits, emerged as feature markers of bipolar disorder.

Data presentation in the literature about the association of mood-stabilizers with different cognitive deficits aims to stimulate the development of criteria for a therapeutic adequacy, meaning to match the mood-stabilizer with specific clinical features in a patient diagnosed with bipolar disorder (age, comorbidities such as dementia or substance related disorders, psychopharmacology history, co-administration of other drugs etc.).

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