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CREATIVE TREATMENT OF BIPOLAR DISORDERS

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SUMMARY

Bipolar disorder is a mental disorder with chronic and remitting course. The disorder is related to high mortality and severely impairs everyday functioning. Therefore a scientifically sound and practical approach to treatment is needed. Making a long-term treatment plan usually also demands some creativity. The patient is interested in a number of issues, from the choice of therapy in acute phases to long-term treatment. Usual questions are how long shall I take the medications, do I really need all those pills or can we decrease the dosage of some drugs? This paper discussed the above mentioned questions in light of latest publications in this field.

Key words: *bipolar disorder – treatment – outcome – polarity - index episode*

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INTRODUCTION

Bipolar disorder is a chronic and usually remitting mental disorder with still largely unexplained etiology and pathophysiology. Even DSM-5 states that "Bipolar and related disorders… are placed between the chapters on schizophrenia spectrum and other psychotic disorders and depressive disorders in recognition of their place as a bridge between the two diagnostic classes in terms of symptomatology, family history and genetics." The mentioned classification still stays with the classic two subtypes of Bipolar disorder I and II and Cyclothymic disorder, while some authors (Akiskal 2003) believe there are several other forms of bipolar disorders. Therefore it is clear that all diagnostic and treatment particularities related to this diagnostic category are far from understood. In everyday clinical practice many questions arise and often the clinician has only few answers to these dilemmas.

Although the exact etiology of bipolar disorder is unknown it is assumed that the onset is influenced by the interaction of genetic and environmental factors. To illustrate the complexity of this relationship a current study (Bauer et al. 2014) confirmed a large, significant inverse relationship between maximum monthly increase in solar insolation and age of onset. These findings remained significant also after controlling for the country median age and the birth cohort. The effect was reduced by half if there was no family history. The effect was one-third smaller for initial episodes of mania than depression.

In the light of above mentioned curiosity it is not uncommon to assume that many factors (biological, genetic, treatment-related, social, economic…) may influence the onset and course of bipolar disorder. Unfortunately many of those factors are not yet known at present.

Treatment of bipolar disorder

It is widely recommended that bipolar disorders should be treated primarily with mood stabilizers. Lithium and sodium valproate are among the most prescribed mood stabilizers, but there are also reports of favorable clinical experience with other antiepileptic drugs like carbamazepine, lamotrigine and some others. In the last years many atypical antipsychotics are said to also have mood stabilizing properties, but clinical experience is still limited. The EMBLEM study (Gonzalez-Pinto et al. 2011) followed up 1076 patients for 2 years after index manic or mixes episode. Less than one third of patients were on olanzapine monotherapy while others received olanzapine in combinations with other drugs. Interestingly, there were no significant differences in remission or improvement parameters. At this moment classical mood stabilizers are still the first choice in treatment and probably cannot be fully replaced with atypical antipsychotics in monotherapy. It is known that some drugs are better in preventing the relapse of manic or mixed episodes while others more efficiently prevent depressive episodes (Tohen & Lin 2006).

The above-mentioned EMBLEM study researched possible gender differences in short-term (12 weeks) and long-term (12 months) outcomes of 2,485 patients experiencing an episode of mania in the course of bipolar disorder. At baseline no significant gender differences in the severity of manic symptoms were found. There were no short-term gender differences in assessment of mania improvement, worsening or recovery, but more women than men showed mania improvement over 12 months (95.4% vs. 89.2%; $p<0.01$). However, more women also developed a depressive episode over 12 weeks (14.9% vs. 9.7%; $p<0.01$) and over 12 months (27.7% vs. 21.5%; $p<0.001$).

Is maintenance therapy really effective?

A recent meta-analysis (Vieta et al. 2011) included 20 studies which met the inclusion criteria (at least 15 patients and 6 months of follow up) with a total of 5364 patients. Eight studies used lithium, 5 quetiapine and others different combinations or other drugs. Very interesting finding was that no monotherapy very efficiently prevented relapse of affective episodes, while the most

efficient proved to be a combination of quetiapine and lithium or valproate. In conclusion the authors state that an effective therapy in acute phase should be continued also in maintenance phase.

Due to known limitations of survival analyses which only allow the study of a single outcome parameter, which is less appropriate in the case of bipolar disorders, a newer statistical method was used. Multi-state outcome analysis of treatments (MOAT) allows to analyze several outcome measures at the same time (remission, subsyndromal states, mixed episodes, tolerance). In this study (Bowden et al. 2015) analyzed two FDA registration studies on lamotrigine, lithium and placebo. Both drugs prolonged remission time, but on the other hand many patients still had some symptoms of depression. Lithium (but not lamotrigine) reduced the duration of mania. In regard to tolerance lithium was very efficient but poorly tolerated, lamotrigine was efficient and well tolerated while placebo proved to be ineffective but excellently tolerated.

An interesting new concept is polarity index. It is known that more than half of patients have more manic or depressive episodes so we are able to determine their prevailing polarity and state the polarity index. Polarity index was not accepted as an additional indicator in DSM-5 but is nevertheless advised to be used as an aid in planning maintenance therapy. Naturalistic studies revealed that patients with prevailing depressive episodes are more frequently treated with antidepressants and mood stabilizers, while patients with more frequent manic episodes usually receive antipsychotics. It is possible to calculate polarity indexes in association with different drugs and clinical features. In patients with manic polarity index type I of bipolar disorder is more frequent, there are more males, patients are usually younger, have an earlier onset of illness, are more frequently hospitalized, have higher substance use and more psychotic episodes. On the other hand patients with depressive polarity index are more frequently diagnosed with type II bipolar disorder, initial episode was usually depressive, associated with stressful events, have more pronounced melancholic features and suicidal behavior (Popovic et al. 2014; Carvalho et al. 2014).

Do we need mood stabilizers in bipolar depression?

On registry data Viktorin et al (2014) investigated 3,240 patients with bipolar disorder who started treatment with antidepressants with or without concomitant mood stabilizers. Nearly 35% of the patients were treated with antidepressant monotherapy. Cox regression identified an increased risk of treatment-emergent mania only in patients on antidepressant monotherapy (hazard ratio=2.83, 95% CI=1.12, 7.19). On the other hand among patients treated with a concurrent mood stabilizer, no change in risk of mania was observed during the 3 months after the start of antidepressant treatment (hazard ratio=0.79, 95% CI=0.54, 1.15). Interestingly, a decreased risk was observed during the period 3-9 months after treatment initiation (hazard ratio=0.63, 95% CI=0.42, 0.93). From these results we can conclude that treating bipolar depression with antidepressant monotherapy is quite common (it was used in more than one third of patients) but cannot be considered a good idea. This is further demonstrated in the following study.

A recent meta-analysis of 24 RCTs in bipolar depression (Selle et al. 2014) demonstrated that pooled drug-over-placebo responder-rate superiority (RR) was moderate (29% (CI: 19-40%)), and NNT was 8.2 (CI: 6.4-11). The apparent efficacy of 10 studied treatments ranked: olanzapine + fluoxetine ≥ valproate > quetiapine > lurasidone > olanzapine, aripiprazole, and carbamazepine; ziprasidone was ineffective, and lithium remains inadequately studied. It should be emphasized that medications were superior to placebo in only 11 of 24 trials (5/5 with quetiapine, 2/4 with valproate), and only lamotrigine, quetiapine and valproate had >2 trials. Contrary to antidepressant monotherapy treatment-associated mania-like reactions were uncommon (drugs: 3.7%; placebo: 4.7%).

Can we predict the response to mood stabilizers?

Even with the best medications, the rate of response is low and the risk of relapse is high. Reliable predictors of individual responses to mood stabilizers are needed and one of the answers seems to be pharmacogenetics research. However, the high expectations are not yet met. Pharmacogenetic studies on the response to lithium found some candidate genes but the results are sparse. The same is true for studies on valproate, lamotrigine or atypical antipsychotics. Existing data no not warrant a change in prescribing practices and further investigation is needed to identify relevant genetic predictors of response. At present the clinical assessment of a subject still plays a major role in treatment however in time the identification of specific individual phenotypic and pharmacogenetic characteristics is likely to become a powerful instrument for the development of personalized therapies (Geoffroy et al. 2014).

How long should the treatment continue?

It has been described that lithium efficacy may fade with time. Although the patient responded well to initial lithium treatment, after several years lithium may become less effective. The mechanism of this effect is not known, there seem to be at least two situations (and probably different mechanisms) when this effect may occur. After discontinuing lithium therapy reinstating lithium may not work anymore, but even on constant therapy with good tolerability lithium may loss its efficacy over time (Post 2012).

What happens in 3 months after treatment discontinuation?

This question was explored in a naturalistic retrospective study of 310 patients with 53 abrupt cessations of at least one drug in 48 patients (Franks et al. 2008). Relapse (mostly mania and hypomania) after discontinuation of a particular drug occurred in 86% for lithium, in 89% for other mood stabilizers, in 64% for atypical antipsychotics and in 58% after cessation of antidepressants.

CONCLUSION

Effectively managing patients with bipolar disorder is a challenge even for the most experienced clinicians. There are several dilemmas in everyday clinical practice which frequently cannot be answered in a simple manner. Traditional mood stabilizers still have a strong place in acute and maintenance therapy while newer drugs, especially atypical antipsychotics are gaining importance also in this field.

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