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NEW STRATEGIES IN THE TREATMENT OF BIPOLAR DISORDER

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INTRODUCTION

About 20-30 years ago the central pillar of psychiatry was schizophrenia. Today´s interest has turned to a new paradigm - bipolar disorder. Knowledge, skills and experiences in treatment of bipolar affective disorder are being enriched with new insights concerning molecular basis of disorder and psychosocial factors importance in its genesis and development, fostering presonalized psyhopharmacotherapeutic and psychotherapeutic treatment approach (Goodwin & Geddes 2007). Increased interest in bipolar disorder has resulted in recognizing the broader group of disorders which have in common periodical affective variability. The lifetime prevalence of type I and type II bipolar disorder is to 2.1% (Dilsaver 2011). In addition to type I and type II bipolar affective disorder and cyclothymia, which together make up 3-4% of today´s general population, this group increasingly encompasses the so-called softer end of the bipolar spectrum. Together, mentioned disorders affect an impressive 5-8% of general population and represent the greatest diagnostic and therapeutic challenge for contemporary psychiatry. The type I and II of bipolar disorder and cyclothymia is not difficult to diagnose, but the bipolarity must be suspected in every early onset unipolar depression, frequent episodes of illness and in positive family history for bipolar and other comorbid disorders. These disorders are: alcoholism and other substance abuse disorders, uncontrollable episodes of rage and violence, suicide attempts and achievements, postpartum depression and psychotic depression. Mentioned states are often resistant to conventional antidepressant therapy or could even worsen and then require special therapeutic approach (Lieber). Recognizing the bipolar affective disorder as heterogenic in its phenomenology, ethiopathogenesis and comorbidity, the significantly increased early diagnostic and has set the path towards new therapeutic strategies. These new strategies in treatment of bipolar affective disorder have been based on its heterogeneity and knowledge on how significant role in occurrence also have negative life events, stressors which through biological connections potentiate immune reactions with inflammatory and metabolic changes causing excitotoxicity in central nervous system. So today, in addition to conventional mood stabilizers, antidepressants and antipsychotics in therapy of bipolar affective disorder are increasingly being introduced adjuvant agents: glutamate transport inhibitors, proinflammatory cytokines inhibitors, cyclo-oxygenase 2 inhibitors, regulators of metabolism and antioxidants (Ghaemi 2000, McInture & Cha 2011). The new strategies in the treatment of bipolar disorder are still being focused on treatment of acute phases (depressive, manic, mixed) and the prevention of new episodes, but emphasizing comparative treatment of cognitive deficits, persistent residual symptoms, comorbid conditions and suicide prevention common in this disorder (Müller-Oerlinghausen et al. 2002). Novel strategies have spurred re-examination of ongoing smoldering dilemma - to follow treatment algorithms or to defer to, for clinician, more challenging personalized approach with greater diagnostic and therapeutic performance along with better suicide prevention and treatment of residual symptoms (Alda et al. 2009).

IMPORTANCE OF EARLY DETECTION AND TREATMENT OF BIPOLAR DISORDER

Bipolar disorder is a recurring disorder in which 46-65% of cases occur before nineteen year old. Early disorder onset has a poor prognosis, course and outcome and is associated with high rates of psychiatric (ADHD, anxiety disorder, personality disorder, alcoholism and other addictions) and physical comorbidity (cardiovascular illness, metabolic syndrome, endocrine disorders, lower back pain, etc.), which moreover contribute to poor outcome. Due to mentioned reasons, there is greater strain in recognizing prodromes of bipolar disorder and early therapy onset (Correll et al. 2007, Kilbourne et al. 2004). This would require changes to be made in current DSM and ICD classifications because current criteria disable such stand. According to current criteria, the majority of bipolar patients have been initially treated for having recurrent depressive disorder. The consequences of late detection and delayed proper treatment are: therapeutic failure, disorder worsening, switching to the opposite phase, the emergence of rapid cyclic form, delay in the implementation of appropriate psychotherapeutic and psychosocial treatments and increased suicide risk. Distinguishing bipolar depression from unipolar depression is not easy. Bipolar depression is marked by: greater affective instability during one episode, prominent motor retardation and prolonged sleep. The unipolar depression is characterized with: insomnia, weight loss and agitation. The stumbling stone in diagnosing bipolar affective disorder lies within restrictive characterization of manic/hypomanic states in

one´s personal history because these states, from patient´s point of view, were often unrecognized of even considered as periods of good health. Therefore, today most bipolar type II patients are treated as unipolar depression, especially if there is no heteroanamnestic data regarding patient´s personal history. In order to attain better recognition of bipolar affective disorder, it is necessary to be tenacious in seeking bipolar psychopathology indicators while differentiating the affective disorders (Bowden 2001). These indicators are noticeable in "softer" portion of bipolar spectrum and for detecting them special diagnostic scale is used, so called Bipolar Spectrum Diagnostic Scale (BSDS) divided in two parts. In the first part the patient responds to 19 statements positively or negatively. These statements describe the main symptoms of bipolar spectrum. Each positive answer carries a point. In the second part, the patient chooses level of symptom severity ranging from 0-6 points (Bipolar Spectrum Diagnostic Scale (BSDS)).

ALGORITHMIC OR PRESONALIZED THERAPEUTIC APPROACH?

Today´s treatment of bipolar affective disorder is mainly founded on compliance to current treatment guidelines, however wide disorder heterogeneity and expanded therapeutic goals were not sufficiently distinguished in these guidelines. Valid guidelines for acute phase symptom alleviation and prevention of new episodes suggest an algorithmic therapeutic approach based on one statistically average bipolar patient whose therapy should be initiated with one drug and if there is no response switch to new one or add it to previous medication. If there is still no response the fourth therapeutic option should be chosen (Yatham et al. 2006, Grunze et al. 2003, Grunze et al. 2004, Kovatch 2005, Young et al. 2004). Many patients could be helped with this approach, however opportunity for help to significant group of patients who would respond only to specific treatment (not provided in algorithms) or ones requiring therapy for symptoms insufficiently recognized in guidelines (neurocognitive deficiency, residual symptoms, suicidality etc.) is being ignored. Therefore, advantages of personalized approach in treatment of bipolar disorder are being accentuated. Guidelines recommendations are not being excluded with this approach but are broadened to "softer" segment of bipolar spectrum and new therapeutic goals (neurocognitive deficiency, residual symptoms, suicidality). For new therapeutic goals the treatment agents are chosen based upon new understandings regarding molecular foundation and psychosocial factors in genesis and development of bipolar affective disorder. Assuming the phenotype heterogeneity due to variability of genetic and epigenetic features as well as individual differences in environment interaction, the symptoms are variable and intertwine with various comorbid mental and physical states. New approach is relied upon pharmacotherapy as vital for treatment of bipolar affective disorder, but also significant role is given to psychoeducation, psychotherapy (interpersonal, family, cognitive-behavioral) and lifestyle management. The main focus is on three treatment aspects: 1. individually and pharmacogeneticaly customized treatment with approved agents; 2. considering new treatment modalities (protein kinase C inhibitors, glycogenic synthase kinase inhibitors, glutamate neurotransmission inhibitors) and 3. improving outcomes targeting so far neglected pathology of bipolar affective disorder such as neurocognitive deficits, residual symptoms and high mortality issue (Alda et al. 2009).

THE MOLECULAR BASIS OF BIPOLAR DISORDER AND NEW TREATMENT STRATEGY

Out of known mood stabilizers palette, only lithium could be highlighted as primary medication for treatment of bipolar disorder. All other medications used for treatment of this disorder primarily belong to other therapeutic groups: anticonvulsants, antipsychotics, antidepressants and anxiolytics. For this reason, the lithium has been distinguished not only as golden therapeutic standard but foundation for generating new agents with similar action mechanism and fewer side-effects. The new therapeutic agents for bipolar affective disorder can be determined bidirectionaly: 1) researching and finding relevant molecular action mechanisms of existing drugs for bipolar affective disorder and designing new medications which will use those mechanisms: 2) researching and revealing the pathophysiology of disease itself and appliance of these cognitions in designing agents who would alleviate, eliminate or inhibit pathologic development. Understanding molecular basis of bipolar affective disorder is somewhat sparse, but there is growing evidence about cell membrane instability and consequential neurotransmitter imbalance possibly underlying bipolar affective disorder. Owing to pathological molecular processes on postsynaptic level respectively second messenger level cell membrane instability occurs. This is corroborated by the results of studying lithium effects on postsynaptic molecular level and since the second messenger system serves for signal transduction of various neurotransmitter pathways it could explain lithium efficacy in different stages of bipolar affective disorder. Therapeutic lithium effect in bipolar affective disorder is obtained on second messenger system levels as follows: 1) inhibition of inositol monophosphatase - weakening the signal transduction in phosphatidylinositol signal pathway and modulating cell response to neurotransmitter system changes; 2) inhibiting the enzyme Glycogen synthase kinase - 3 (GSK-3) - component of many signal pathways with diverse effects when inhibited; 3) cyclooxigenase 2 inhibition which mediates arachidonic acid cascade (Atack et al. 1995,

Rapoport & Basetti 2002, Quiroz et al. 2004). Other mood stabilizers act on different enzymes involved in postsynaptic signal transduction and those action mechanism serve as basis for designing new medications. The alterations on second messenger level are the consequence of genetic and epigenetic factors respectively to changes in stress response system triggering certain episodes. Various stressors lead to disruptions of hypothalamic-pituitary-adrenal axis on different levels and may also cause changes on glutamate and other neurotransmitter transport in central nervous system. Therefore, in bipolar affective disorder distinct psychoactive agents could be efficient. Still, primary medications in therapy of this disorder should be mood stabilizers designed for entering the core of disorder pathophysiology. Researched candidates are: glucocorticoid synthesis inhibitors, antagonists of glucocorticoid receptors (Mifepristone (RU-486), antagonists of CRF 1 receptors (Antalarmin). Since the glutamatergic system is especially involved in pathophysiology of affective disorder possible therapeutic agents are being investigated among glutamate receptor modulators, NMDA antagonists (lamotrigine, riluzole, memantine, Felbamat, Zinc) and AMPA receptor modulators (Ampalex). With significant changes in brain neuroplasticity being found concerning bipolar affective disorder, along with previously mentioned, agents for modulation of neurotrophic cascades, involving NGF and BDNF (phosphodiestherase inhibitors) are being tested. These agents should prevent degenerative changes in nervous system and consequential chronification with permanent cognitive deficiency and residual symptoms of affective disorder. Ideal drug for bipolar disorder should be effective for: a) acute mania/hypomania, depression and mixed states treatment and without significant side-effects; b) therapy of acute rapid cycling episodes; c) elimination of subsyndromal and residual affective syndromes: d) elimination of psychotic symptoms in acute affective episodes; e) prevention of relapses and new episodes; f) suicide prevention; g) comorbid states reduction; h) chronification prevention; i) precluding cognitive deficiency; j) restoring full social and labor activity. Naturally, in the near future, such magic molecule would not be found but we are all witnesses of major shifts towards this ideal (Zarate et al. 2006, Gould et al. 2004, Coyle & Duman 2003).

CONTEMPORARY APPROACH TO TREATMENT OF BIPOLAR DISORDER

The bipolar affective disorder is characterized by clinical, genetic and pathophysiological heterogeneity and treatment often requiring personalized approach. Monotherapy represents rarely attainable ideal. Most often used combination in practice is combination of mood stabilizers with atypical antipsychotics or antidepressants. The disorder´s clinical course demands pharmacotherapeutic adjustment for actual episode or disorder phase and new episodes prevention. Special attention is focused on psychoeducation and specific psychotherapy as necessary strategies for ensuring treatment adherence (Alda et al. 2009).

Acute pharmacological treatment

In practice, pharmacotherapeutic approach should be adjusted to features of bipolar affective disorder regardless having mostly manic or depressive episodes.

Bipolar disorder stabilizers with predominantly manic episodes

First-line mood stabilizers of manic episodes are: lithium, sodium valproate, divalporex (seminatrium valproate), carbamazepine and second generation antipsychotics. Second-line treatment options are: clonazepam, lorazepam and some other benzodiazepines (Alda et al. 2009, Yatham et al. 2006, Grunze et al. 2003, Grunze et al. 2004, Kovatch 2005, Young et al. 2004, Rush et al. 2000). All second generation antipsychotics are suitable for treatment of acute manic episodes but as adjunct therapy for alleviation of psychotic symptoms. As the least risky for switching into depressive episode are: olanzapine (McElroy et al. 1998), quetiapine (Vieta et al. 2002), risperidone (Sherk et al. 2007), and aripriprazole (Vieta et al.).

Bipolar disorder stabilizers with predominantly depressive episodes

In the treatment of depressive episode as first-line agents are mentioned these mood stabilizers: lamotrigine, lithium, olanzapine-fluoxetine combination and electroconvulsive therapy (ECT). The FDA has approved quetiapine and olanzapine-fluoxetine combination for bipolar depression treatment. Second-line mood stabilizers are: bupropion, paroxetine, venlafaxine and some other new antidepressants (Alda et al. 2009, Yatham et al. 2006, Grunze et al. 2003, Grunze et al. 2004, Kovatch 2005, Young et al. 2004, Rush et al. 2000, Goldsmith et al. 2003).

Practical implications

Mood stabilizers have been applied in treatment of bipolar affective disorder (BAD) according to current guidelines from particular psychiatric associations and expert concensus groups. They generally help the physicians concluding the best treatment choice in particular clinical situations. The guidelines do not contain full concensus nor do they recommend agent approved only by FDA or EMEA, so the "off-label" recommendations are not rare. Either way, there is no ideal mood stabilizer who would have rapid onset on all bipolar affective disorder forms, enhance cognitive functions, eliminate residual symptoms and be successful in maintaining remission with good tolerability and easy usage. Because of this, the practice combines several medications and drug choice is adjusted to clinical and genetic patient profile. Advantage of monotherapy is in therapeutic clarity and better treatment result interpretability. Combined the-

rapy ensures manifestation of individual therapeutic skill and better adjustment to patients genetic and clinical profile. Only a certain percentage of patients responds favorably to specific drug. Adding drug more, increases the probability of favorable therapeutic response. Although, guidelines suggest initial monotherapy (lithium or valproate in mania or lamotrigine in depression) if the patient is agitated or psychotic there is no need to hesitate but introduce combination of lithium or anticonvulsants with second generation antipsychotic (for example, lamotrigine + olanzapine) because the complex clinical presentation requires complex treatment approach (Perlis 2005, Fountoulakis et al. 2007). Special caution is recommended when applying antidepressants regarding possible switch to manic episode. For this reason, the antidepressants are used in acute depressive episode as part of combined therapy and should be excluded after depressive symptoms retrieve. This is particularly important concerning tricyclic antidepressants and monoamino oxidase inhibitors. The selective serotonine reuptake inhibitors are less potent in causing switch to manic episode and some of them are used more freely for mood stabilization. The effectiveness in bipolar depression have shown paroxetine and bupropione, alone or combined with antipsychotic or anticonvulsant (Alda et al. 2009, Perlis 2005, Suppes & Kelly 2006). Ghaemi and associates (2003) in literature about applying antidepressants in bipolar affective disorder had found the following: 1) high risk of rapid cycling episodes when on antidepressants; 2) unlike lithium, antidepressants were not significantly preventing suicide risk in bipolar affective disorder; 3) the antidepressants have had less efficacy compared to mood stabilizers in acute bipolar depression and were less efficient in relaps and new episode prevention; 4) mood stabilizers, particularly lithium and lamotrigine, shown effectiveness in acute and prophylactic therapy of bipolar depressive episodes. Based on these findings they made the following conclusions: a) the antidepressants had shown significant risk of mania and long-term deterioration due to frequent rapid cycling episodes; b) antidepressants should not be routinely applied in mild to moderate bipolar depressions; c) antidepressants should be excluded after acute episode withdrawal or maintain them during treatment only when depressive episodes occur repeatedly. In other words, no one prohibits usage of antidepressants in bipolar depression but rational and cautious approach regarding possible consequences of such therapy is required (Ghaemi et al. 2003). Mixed episodes bipolar disorder and rapid cycling one represent particular therapeutic challenge. The FDA has approved carbamazepine and most of the atypical antipsychotics (olanzapine, risperidone, aripriprazole, ziprasidone) for mixed episodes therapy but often used are also valproate and lamotrigine. Preferably the antidepressants should be avoided due to risk of mood destabilization. In therapy of rapid cycling episodes all agents which might mitigate these states should be eliminated or reduced. This applies particularly to antidepressants. Treatment should be applied with appropriately selected a mood stabilizer (lithium, valproate, lamotrigine, carbamazepine) in combination with atypical antipsychotics, or high doses of thyroid hormone (Alda et al. 2009, Suppes & Kelly 2006, Calabrese et al. 2000). The lithium has shown efficacy in suicide risk reduction (Baldessarini et al. 2006). A particular problem is treatment of refractory bipolar affective disorder, most frequently refractory bipolar depression. Lamotrigine has found to be most successful, and experiments regarding combination of sleep deprivation and light therapy are still being investigated (Nierenberg et al. 2006, Benedetti et al. 2005). A number of new anticonvulsants with mixed, negative or unproven efficacy for therapy of bipolar affective disorder are being researched (gabapentine, pregabaline, tiagabine, levetiracetame, oxcarbazepine, phenytion, topiramate, zonisamide) (Yatham 2004, Evins 2003).

Strategies for bipolar disorder prevention

Pharmacotherapy

Prevention strategies of bipolar disorder distinguish relaps prevention and prophylaxis. After suppressing acute symptoms of this disorder (pathological affect, aggressiveness, self-deliberation symptoms, hyperactivity, psychotic symptoms, sleep disturbances) maintenance therapy continues marked by lowest possible dosage for prevention of new episode onset, presservation of cognitive functions and lifestyle quality. This presumes progressive dose reduction and preferably monotherapy with subsequent exclusion of other medications. Only after all symptoms withdrawal, that is restoration of euthymic state without residual symptoms, prophylactic therapy could be approached. Traditionally, the prophylactic treatment was recommended if there were existing evidence about earlier frequent episodes. Recently, the prevention onset is suggested to be as early as possible, even after first manic episode. In bipolar affective disorder type II the initiation of preventive treatment depends on frequency of depressive and manic episodes. The primary therapeutic agent is still lithium although valproate is frequently used. Controlled studies suggest atypical antipsychotics as successful preventive agents, especially in recurrent episodes with psychotic symptoms. For most of depressive episodes of bipolar affective disorder the lamotrigine has been recommended. The antidepressants in bipolar affective disorder prophylaxis should be avoided (Alda et al. 2009, Ghaemi et al. 2004).

Psychoeducation and psychotherapeutic techniques

The treatment of bipolar affective disorder could be compared with shooting the moving target wherefore course changes are determined by unpredictable life stressors and negative life events (divorce, loss of a loved ones, job loss etc.), changes in social rhythm (job

change, moving, marriage etc.) along with treatment changes and its discontinuation. Pharmacotherapeutic adjustment is not sufficient for bipolar affective disorder episode prevention. That is why new therapeutic strategies of bipolar affective disorder comprehend various psychotherapeutic interventions aimed at minimizing unexpected changes during course of bipolar disorder in order to ensure maximal therapeutic success with pharmacologic treatment. Application of particular techniques depends upon treatment phase (Frank et al. 2000). Psychoeducation should be commenced early, as soon as the patient state allows it, and continued during therapy. This treatment represents not merely informing the patient regarding illness and medications but complex technique which encompasess training to cope with chronic illness and other frequent comorbid conditions, lifestyle regulation, acquiring positive habits, recognizing prodromes and realizing the importance of treatment adherence in order to prevent relapses and new episodes (Colom et al. 2003, Vieta & Colom 2004, Lam et al. 2005).

Most frequently used psychotherapeutic techniques are: the social rhythm therapy, interpersonal therapy, cognitive-behavioral therapy and family oriented therapy. Social rhythm therapy is based on chronobiological model of bipolar disorder which presumes persons with this disorder to have congenital instability of chornobiological rhythm and require systemic encouraging. Beside psychoeducation, this technique is suitable for bipolar affective disorder with predominant manic episodes. The interpersonal therapy was developed by Klerman in early seventies as most appropriate psychotherapeutic treatment for patients with bipolar depression respectively bipolar affective disorder with predominant depressive episodes. Interpersonal therapy, in such type of disorder is applied with cognitive-behavioral therapy and family oriented therapy (Frank et al. 2000, Lam et al. 2005, Miklovitz 2008, Miklovitz et al. 2007, Miklovitz et al. 2000).

Psychoeducation and psychotherapy assist patients suffering from bipolar affective disorder and their families in dealing with this chronic disease, prevention of new episodes and greater treatment adherence, which provides better pharmacotherapeutic efficacy and stabilizes that improved state. The psychotherapeutic treatment, as significant component for integrative therapeutic approach in managing bipolar affective disorder, is essential during prolonged treatment phase and ambulatory prophylaxis (Miklowitz 2006).

CONCLUSION

New strategies in the treatment of bipolar disorder acknowledge the genetic and clinical heterogeneity and importance of psychosocial factors regarding genesis and disorder development. Regardless still being focused on acute phase treatment (depressive, manic, mixed) and new episode prevention, more attention is given to treatment of cognitive deficits, persistent residual symptoms, comorbid states and suicide prevention. These guidelines have broaden to "softer" segment of bipolar spectrum and new therapeutic goals (neurocognitive deficits, residual symptoms, suicidality). Pharmacotherapy has remained vital in therapy of bipolar affective disorder, however now with integrated techniques of psychoeducation, psychotherapy and patients lifestyle alterations. There are three main aspects of novel pharmacotherapeutic approach: 1. individually and pharmacogeneticaly customized treatment with approved agents; 2. considering new treatment modalities (protein kinase C inhibitors, glycogenic synthase kinase inhibitors, glutamate neurotransmission inhibitors) and 3. improving outcomes targeting so far neglected pathology of bipolar affective disorder such as neurocognitive deficits, residual symptoms and high mortality. Most frequently used psychotherapeutic techniques are: social rhythm therapy, interpersonal therapy, cognitive-behavioral therapy and family oriented therapy.

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