Enigma of Bipolar depression

Bipolinės depresijos mįslė

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SUMMARY

Bipolar disorder is a prevalent and disabling mental disorder. Annual prevalence rates vary from 1–6% depending on the diagnostic criteria used in the studies. Substantial part of the bipolar disorder is spent in depressive phase of the illness. The clinical picture of it resembles that of Major depressive disorder, what causes difficulties in making an appropriate diagnosis and selecting effective treatment. Several studies found relatively high percentage of diagnose conversion for patients with diagnosis of depressive episode at index admission 12,9–49 %. The higher rate in family history of mental disorders, especially bipolar disorders, younger age of onset of first depression, more atypical symptoms like hypersomnia and weight gain; higher rate of suicidal attempts, recurrence and hospitalisations; more complex temperamental dysregulations could help to recognise bipolar depression.

The therapeutic management of bipolar disorder may be extremely complex, because of the episodic course, the usually severe disability associated with the acute manic and especially depressive phases of illness.

Conventional mood stabilisers and antidepressants are frequently prescribed for the acute and prophylactic management of bipolar depression. This prescription patterns continues despite proofs of their limited efficacy and risks of inducing mood swings. Several novel treatments, such as third-generation anticonvulsants, atypical antipsychotics and dopamine agonists have been actively studied for this indication.

Based on the current published evidences lithium, lamotrigine and quetiapine monotherapy, olanzapine plus selective serotonin reuptake inhibitors (SSRI), and lithium or divalproex plus SSRI/Bupropion continue to remain the first-line options for the management of bipolar depression.

Key words: bipolar depression, anticonvulsants, antidepressants, atypical antipsychotics.

SANTRAUKA

Bipolinis sutrikimas – paplitusi negalią sukelianti psichikos liga. Metinis sergamumas svyruoja nuo 1 iki 6 proc. bendros gyventojų populiacijos, – priklausomai nuo to, kokie diagnostiniai kriterijai naudojami tyrimų metu. Pagrindinę bipolinio sutrikimo trukmės dalį užima depresijos fazė. Klinika panaši į didžiosios depresijos, o tai sukelia sunkumų diagnozuojant ir parenkant veiksmingą gydymo būdą. Keletas tyrimų nustatė santykinai didelį depresija sergančių pacientų diagnozių pakeitimo procentą, kai priimtinas rodiklis yra 12,9–49 proc. Bipolinę depresiją gali padėti atpažinti tokie veiksniai, kaip psichikos ligos šeimos anamnezėje, ypač bipolinis sutrikimas; jaunesnis amžius pirmąkart susirgus depresija; daugiau atipinių simptomų, tokių kaip hipersomnija ir svorio priaugimas; daugiau suicidinių bandymų, recidyvai ir hospitalizacijos; sudėtingesnis temperamentas.

Bipolinio sutrikimo gydymas gali būti ypač sudėtingas dėl epizodinės eigos, paprastai gana sunkaus neįgalumo, susijusio su ūmine manija, o ypač dėl šios ligos depresijos fazių.

Ūminei būklei gydyti ar bipolinės depresijos prevencijai dažnai yra skiriami įprastiniai nuotaikos stabilizatoriai ir antidepresantai. Toks gydymas vis tebeskiriamas, nepaisant įrodymų apie šių vaistų ribotą veiksmingumą ir galimai sukeliamus nuotaikų svyravimus. Šioms indikacijoms gana aktyviai tiriama keletas naujų medikamentų, tokių kaip trečios kartos vaistai nuo epilepsijos, atipiniai antipsichotikai ir dopamino agonistai.

Remiantis dabar skelbiamais įrodymais, ličio, lamotrigino ir kvetiapino monoterapija, olanzapino ir selektyviųjų serotonino reabsorbcijos inhibitorių (SSRI) derinys ir ličio ar divalproekso derinys su SSRI/bupropionu išlieka pirmos eilės vaistais gydant bipolinę depresiją.

Raktažodžiai: bipolinė depresija, vaistai nuo epilepsijos, antidepresantai, atipiniai antipsichotikai.

INTRODUCTION

The term bipolar disorder describes usually episodic and clinically sometimes extremely severe and dramatic presentation. Bipolar disorder encompasses several phenotypes. Cross-sectionally, bipolar patients may present with either depressive, or manic or hypomanic episodes; additionally a wide spectrum of other psychopathological features may be present. This considerable cross-sectional phenotypic heterogeneity continues to be the source of some controversy and the exact clinical characteristics of bipolar disorder are subject to debate. The core diagnostic criterion of bipolar disorder is the presence of a manic syndrome, defined as a period in which the person suffers from unusually and clinically significant extreme good mood or irritability and experiences a number of explicitly defined associated symptoms (i.e. decreased need to sleep, hyperactivity and impaired control). Although, typically, patients with a manic episode also experience major depressive episodes, bipolar disorder can be diagnosed even if only one manic episode and no past major depressive episodes are present, in such a cases diagnosis of Bipolar disorder type I is assigned. Another disorder type is Bipolar disorder type II, which differ form type I only by presence of hypomanic but no manic episodes. Hypomanic episodes differ from mania by a shorter duration (at least 4 days instead of 1 week), and less severe impairment (not severe enough to cause marked impairment in social or occupational functioning, psychiatric hospitalization, or psychotic features).

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The epidemiology of bipolar disorder has been addressed in several studies in Europe [1, 2]. The prevalence estimates for any bipolar disorders range from less than 1% to over 5%. This variation seems to be largely dependent on the type of study, the diagnostic coverage and the type of assessment instrument used. Prospective-longitudinal studies tend to report higher rates, possibly because they are more sensitive in catching the lifetime history. The 12-month prevalence of bipolar I disorder is usually estimated to be around 1%, and on average similarly high for hypomania (bipolar II, 1,2%). Bipolar II prevalence findings show much more variation with estimates up to 6%, especially if cyclothymia – a trait-like variant – and other bipolar-spectrum like conditions are considered. Some authors suggested to separate additional forms of bipolar disorders like types III and IV [3].

Bipolar disorder usually takes a recurrent and severe course with an increasing number of manic, depressive and missed episodes of variable severity and duration over the patient's lifetime. The majority of patients with bipolar I will frequently receive drug treatment over their lifetime to prevent further episodes. Over 60% of all patients affected will require hospitalization during the course of their disorder. The therapeutic management of bipolar disorder may be extremely complex, because of the episodic course, the usually severe disability associated with the acute manic and especially depressive phases of illness. The article will review efficacy of different treatment options in the management of depressive phase of bipolar disorder.

PREVALENCE AND CLINICAL FEATURES OF BIPOLAR DEPRESSION

Patients with Bipolar disorders presented one or other type of affective symptoms almost half of their lives over 13 years of observation. Depressive symptoms accounted from 67 to 93 % of time spend in ill state [4, 5]. The depressed phase of Bipolar disorder, albeit usually much less colourful than mania, is more likely to lead to psychosocial impairments and shorten lives.

Several studies found relatively high percentage of diagnose conversion for patients with diagnosis of depressive episode at index admission 12,9–49 % [6–9]. By the 15-year follow-up, 27% of the study group had developed one or more distinct periods of hypomania, while another 19% had at least one episode of full bipolar I mania in one study [9].

French multi-centre study (EPIDEP), repeatedly assessed soft bipolarity symptoms in the population of 537 patients, found higher rate in family history of mental disorders, especially bipolar disorders, younger age of onset of first depression, more atypical symptoms like hypersomnia and weight gain; higher rate of suicidal attempts, recurrence and hospitalisations; more complex temperamental dysregulations [7].

The authors in a recent study, comparing 477 subjects with a diagnosis of bipolar disorder and 1,074 with major depressive disorder, found that Bipolar depression was associated with family history of bipolar disorder, an earlier age at onset, a greater previous number of depressive episodes and more common fears. Whereas sadness; insomnia; intellectual (cognitive), somatic (muscular), respiratory, genitourinary complaints; and depressed behaviour were more common in patients with unipolar depression. A logistic regression model correctly classified 86,9% of the subjects [10].

TREATMENT OPTIONS FOR BIPOLAR DEPRESSION

Mood stabilisers

Mood stabilisers are the cornerstone of the treatment of bipolar disorders. They were the only first-line options for monotherapy for bipolar depression up to very recent times.

Lithium

Eight of nine double-blind trials versus placebo suggest that lithium is superior to placebo in treating bipolar depression [11]. However, most of these trials are methodologically questionable. Only a meta-analysis of these studies has sufficient patient numbers to confirm the efficacy of lithium [12]. The strength of the antidepressant effect of lithium monotherapy compared to that of other antidepressants also remains rather unclear. Five rather small double blind trials have been documented (for a review, see [13]). I am not aware of published controlled trials comparing the antidepressant efficacy of lithium with that of antidepressants of the new generation head to head. Although lithium is also used as an augmentation strategy in refractory depression, lithium monotherapy by itself may not be sufficient in patients with moderate to severe bipolar depression.

Valproate

Previously, support for divalproex monotherapy for bipolar depression was available only from uncontrolled trials. A prospective, open-label study in 19 patients with bipolar II disorder, depressed phase, demonstrated an antidepressant effect of valproate especially in medication naive patients [14]. This strategy has now shown efficacy in two small randimised placebo-controlled study (RCT) in Bipolar depression [15, 16]. A large-scale, placebo-controlled maintenance study showed that valproate, but not lithium, was significantly better than placebo in preventing a depressive relapse [17]. However, this was a secondary analysis of a trial that failed on its primary outcome measure.

Carbamazepine

Similar to valproate, carbamazepine has been much less studied in the treatment of acute bipolar depression than in mania and prophylaxis. The majority of studies again mixed unipolar and bipolar depressed patients. Some trials suggested moderate efficacy [18, 19], including one placebo-controlled trial [20], but others did not replicate this [21]. In the latter trial, the response rate for carbamazepine did not appear to be better than that expected for placebo. Thus, similar to valproate, carbamazepine is not to be recommended as a monotherapy for bipolar depression, although it may be helpful to prevent a switch into mania.

Lamotrigine

Of all available so-called mood stabilisers, lamotrigine is supported by the largest trials suggesting acute antidepressant efficacy. Although, it failed to show significance for the primary outcome variable, namely the Hamilton Depression

Scale, against placebo [22], other ratings (Montgomery-Asberg-Depression-Scale, CGI) were significantly in favour of lamotrigine. The second large RCT showed that about 52% of patients responded, which was twice that seen in the placebo group [23]. Further, a recent RCT in patients who had breakthrough bipolar depression while on lithium showed that lamotrigine add-on was significantly superior to placebo add-on in treating depressive symptoms as indicated by significantly greater improvements in MADRS scores [24]. Unfortunately, at present there is no controlled trial published comparing lamotrigine with a standard antidepressant.

Adjunctive strategies

Adjunctive lamotrigine. Although there was no previous controlled trial evidence for lamotrigine as an add-on to lithium or divalproex, the addition of lamotrigine was recommended as second line option in one recent guidelines [25]. This strategy is now supported by a small RCT reporting that the addition of lamotrigine was as effective as adding an SSRI to lithium or divalproex for patients with bipolar depression [26]. A more recent larger RCT also now supports this strategy [24]. In the STEP-BD study, lamotrigine was numerically more effective than inositol or risperidone for patients with treatment-resistant bipolar depression already receiving combination therapy with lithium, divalproex or carbamazepine plus an antidepressant [27].

Adjunctive topiramate. A single-blind trial suggested that adjunctive topiramate was as effective as adjunctive bupropion when added to ongoing therapy with divalproex, lithium or atypical antipsychotics [28].

Adjunctive zonisamide. A chart review was conducted of naturalistic treatment with zonisamide in 35 persons with bipolar disorder taking standard mood stabilizers and other psychotropic agents, adjunctive zonisamide appears to have modest benefit in global improvement [29].

*Adjunctive riluzole***.** Preliminary, open-label data suggest that adjunctive riluzole may improve bipolar depression when added to lithium therapy [30].

Adjunctive pramipexole. The dopamine agonist pramipexole was found to have good antidepressant effects in two small placebo controlled randomised trials in patients with bipolar depression [31, 32].

Adjunctive eicosapentaenoic acid. In a 12-week RCT in 85 patients with bipolar depression, adjunctive eicosapentaenoic acid (EPA) was more effective than placebo in improving depressive symptoms [33]. But another study did not find overall evidence of efficacy for adjunctive treatment with EPA [34].

Antidepressants

The use of antidepresants in the treatment of bipolar depression is a continuous area of controversies. Food and Drug Administration (FDA) has not approved any of the more than 25 standard antidepressants for the treatment of bipolar depression. However, standard antidepressants are commonly used as adjuncts to mood-stabilizing medication for the treatment of bipolar depression, despite limited evidence of the short-term and long-term efficacies and the putative risk of treatment-emergent mania or hypomania.

Long-term continuation of initiated antidepressant treatment showed decreased the risk of depressive relapse in patients with bipolar illness in one study [35]. In a 6-month RCT in patients with BD II and bipolar not otherwise specified who had responded to fluoxetine, relapse rates were 43% with continued fluoxetine and 100% with placebo, but the sample size was too small to show statistical significance. Although no hypomanic switch was observed, there was a significantly greater mean increase in manic symptom scores with fluoxetine [36].

In a placebo-controlled study in which subjects using therapeutic doses of the mood stabilizer lithium were randomly assigned to receive concurrent treatment with a standard antidepressant (paroxetine or imipramine) or placebo, those receiving lithium plus an antidepressant did not have a significant advantage over those receiving lithium plus placebo [37]. The only large positive trial of standard antidepressant treatment for bipolar depression published to date involved the combination of olanzapine and fluoxetine, which was superior to placebo as well as to olanzapine alone [38]. However, the study did not address the effectiveness of standard antidepressants used in conjunction with lithium or valproate.

The recent double-blind of The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study equal number of patients (23,5%) receiving a mood stabilizer plus adjunctive antidepressant therapy had a durable recovery, as did 51 patients (27,3%) receiving a mood stabilizer plus a matching placebo (P=0,40) [39].

The Stanley Foundation Bipolar Network study addressed comparative efficacy of different new generation antidepresants in the treatment of bipolar depression. Using outcome criteria corrected for rates of treatment-emergent affective switch, they reported that 33,3% of patients with bipolar depression had a response to treatment with bupropion, 41,4% had a response to sertraline, and 35,6% had a response to venlafaxine, in between group differences were not statistically significant [40].

Treatment-emergent switch into mania

Prescription of antidepressants for bipolar patients always carries certain risk of polarity switch. Some early studies found higher rates of treatment-emergent switch into mania in bipolar patients treated with tricyclic antidepressants (TCAs) and monoaminoxidase inhibitors (MAOs) than with selective serotonin re-uptake inhibitors (SSRIs) or placebo [41, 42]. The double-blind comparison of bupropion, sertraline, and venlafaxine by the Stanley Foundation Bipolar Network, one of the largest trial in this field, found a significantly higher rate of switch from depression to mania or hypomania among subjects receiving venlafaxine than among those receiving bupropion or sertraline [43].

Neither paroxetine nor bupropion was associated with an increased rate of treatment-emergent affective switch in STEP-BD study [39]. These results are largely in agreement with those from studies that associate selective serotonin-reuptake inhibitors and bupropion with lower rates of treatment-emergent affective switch than venlafaxine or

desipramine [44, 45].

The findings from another STEP-BD study found, that in bipolar depression accompanied by manic symptoms, antidepresants do not hasten time to recovery relative to treatment with mood stabilizers alone, and treatment with antidepresants may lead to greater manic symptom severity [46].

Antipsychotics

Clinical qualities of Second Generation Antipsychotics have expanded their use not only in schizophrenia and other psychotic, but also in affective and anxiety disorders. Over the recent years several studies have been carried on also in the treatment of bipolar depression.

Olanzapine

In the first double-blind, 8-week, RCT 833 adults with bipolar I disorder were randomly allocated to the treatment with olanzapine, olanzapine-fluoxetine combination or placebo. Olanzapine was found to be more effective than placebo, and combined olanzapine-fluoxetine was found to be more effective than olanzapine and placebo [38]. A second, large RCT has now assessed this combination [47]. In a 7-week RCT, the combination of olanzapine and fluoxetine was as or more effective than lamotrigine, but lamotrigine was better tolerated. Olanzapine plus fluoxetine was associated with statistically significantly greater improvement in depressive and manic symptoms compared to lamotrigine. However, effect sizes were small (0,24–0,26) and there were no differences in response rates.

One of the criticisms of the original study was that it did not include a fluoxetine alone treatment regimen, which raised the possibility that the olanzapine plus fluoxetine combination may be no more effective than fluoxetine alone. A small, recent RCT did include both monotherapy groups, as well as the combination, but failure to detect differences in improvements in depressive symptoms between groups, including the placebo group, were attributed to inadequate sample size [48].

Quetiapine

The first double-blind, placebo controlled BOLDER study assessing efficacy of quetiapine monotherapy in bipolar depression has recently been published [49]. In this report, the effect size on Montgomery Asberg Depression Rating Scale (MADRS) in the bipolar I sample was very large (1,09 and 0,91 on 600 and 300 mg, respectively), with a smaller effect size in the bipolar II sample (0,39 and 0,28, respectively). Remission rates were 52,9% in the groups taking 600 mg/day and 300 mg/day of quetiapine compared to 28,4% for placebo [49].

Recently published 8 week, double-blind BOLDER II study of 509 patients, showed significant benefit in the patients with bipolar II depression. Therapeutic effect sizes at Week 8 were 0,61 and 0,54 for quetiapine 300 and 600 mg/d, respectively [50].

A post hoc analysis, pooling the patients with bipolar II depression from both BOLDER trials, demonstrated benefits in both rapid and non-rapid cycling depression, with a moderate effect size on MADRS of 0,54 in those on 600 mg and 0,45 in those on 300 mg [51].

Other antipsychotics

Open label adjunctive strategies of other antipsychotics have been assessed in two recently published studies.

Participants (N=66) with treatment-resistant bipolar depression from STEP-BD programme were randomly assigned to open-label adjunctive treatment with lamotrigine, inositol, or risperidone for up to 16 weeks. Risperidone showed the lowest and very small recovery rate, although no statistically significant difference between the groups were found on primary efficacy measure [27].

Open adjunctive aripiprazole was administered to 30 outpatients with treatment-resistant bipolar depression defined by STEP-BD Affective Disorders Evaluation. Following treatment for a mean duration of 84 ± 69 days, 8/30 (27%) patients responded and 4/30 (13%) remitted according to the CGI-S criteria [52].

Non pharmacological treatments

An RCT reporting on 5-year follow-up results found that a 21-week group psycho education program as adjunct to standard pharmacological management significantly reduced the rate of relapse of both hypo/manic and depressive episodes [53].

In an RCT examining the role of adjunctive Cognitive-behavioural therapy (CBT) for relapse prevention over 30 months, patients in the CBT group had significantly fewer days in bipolar episodes; however, CBT had no significant effect on relapse reduction after the first year [54]. Similarly, in an RCT of CBT in 253 patients, more than half the patients had a recurrence by 18 months, with no significant differences between groups [55]. Post hoc analyses showed that a small group of patients with fewer than 12 lifetime episodes did experience a benefit from the intervention. Together, these two trials suggest that the long-term effectiveness of CBT may be limited, but the role of booster sessions in maintenance of efficacy needs further exploration.

In a comparison of Interpersonal and social rhythm therapy (IPSRT) to intensive clinical management, there was no difference in the time to stabilization of acutely ill patients with BD [56]. However, over the 2-year follow-up, patients treated with IPSRT acutely had a significantly lower rate of recurrence whether they continued IPSRT or were switched to intensive clinical management.

Eighty-four of 152 depressed outpatients with bipolar I or bipolar II disorder in the multisite STEP-BD study were randomly assigned to intensive psychosocial intervention (30 sessions over 9 months of interpersonal and social rhythm therapy, cognitive behavioural therapy [CBT], or family-focused therapy), and 68 patients were randomly assigned to collaborative care (a 3-session psycho educational treatment). Patients in intensive psychotherapy had better total functioning, relationship functioning, and life satisfaction scores over 9 months than patients in collaborative care [57].

CONCLUSIONS

Based on the current published evidences lithium, lamotrigine and quetiapine monotherapy, olanzapine plus selective

serotonin reuptake inhibitors (SSRI), and lithium or divalproex plus SSRI/Bupropion continue to remain the first-line options for the management of bipolar depression.

Modern antidepressants are relatively safe in the treatment of bipolar depression, but appear to have limited efficacy in RCTs. Antidepressants should be prescribed with mood stabilisers, which could attenuate risks of treatment-emergent affective switches.

First-line options in the maintenance treatment of bipolar disorder continue to be lithium, lamotrigine, valproate and olanzapine-fluoxetine combination. New data also support quetiapine monotherapy as a second-line option for the management of bipolar II depression. There is recent evidence to support the use of olanzapine as a second-line maintenance therapy for bipolar depression. When antidepressants are effective, the duration of maintenance therapy should be determined on a case-by-case basis.

Psychosocial interventions for maintenance therapy are associated with reduction in overall rates of relapses, especially in depressive phase of illness.

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