NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

REVIEW

Arch Neuropsychiatry 2021; 58: (Supplement 1): S31–S40
https://doi.org/10.29399/npa.27408

Acute and Maintenance Treatment of Bipolar Depression

Evrim ERTEN

Altinbaş University School of Medicine, Department of Psychiatry, İstanbul, Turkey

ABSTRACT

The World Health Organization reported a lifetime prevalence of 2.4% for BD-I, BD-II and sub-threshold types of bipolar disorder (BD). Depressive episodes are more common than manic episodes for many BD patients. Studies show that depressive mood persists in 2/3 of life, even if they are under treatment. It may be difficult to diagnose BD in the event of depression in the first episode. The correct diagnosis and the treatment can be delayed for 6–8 years, and even longer if disorder starts in adolescence. It is reported that 40% of the patients who were initially diagnosed as unipolar were later diagnosed as BD. The features that enable us to diagnose BD depressive episode: 1) family history of BD or psychosis 2) early onset with depression 3) cyclothymic temperament characteristics 4) four or more depressive episodes in 10 years 5) agitation, anger, insomnia, irritability, excessive talkativeness or other 'mixed' or hypomanic features or psychotic symptoms during depressive episode, 6) clinical 'worsening' caused by the appearance of mixed symptoms after AD treatment 7) suicidal thoughts and attempts 8) substance abuse 9) hypersomnia in the depressive episode or sleeping too much during the day, overeating, psychomotor agitation. The number of studies conducted on BD depressive treatment is limited, the information was obtained by excluding this group from the studies or by compiling the information obtained from the treatment of unipolar depression. In this review, acute and maintenance treatment of the depressive episodes of BD will be discussed according to the treatment algorithms.

Keywords: Bipolar disorder I, bipolar disorder II, treatment

Cite this article as: Erten E. Acute and Maintenance Treatment of Bipolar Depression. Arch Neuropsychiatry 2021; 58 (Suppl 1): S31-S40.

INTRODUCTION

Bipolar disorder (BD) is a mental illness that includes significant risk of morbidity and mortality, and its prevalence in the population varies. The World Health Organization (WHO) reported lifetime prevalence of 2.4% for BD-I, BD-II and BD sub-threshold types. For BD depressive episode, DSM-5 criteria do not differ from those of DSM-IV. The diagnosis of depression is made after the presence of depressed mood and/or anhedonia for at least 2 weeks and at least 4 of the symptoms that includes changes in sleep, appetite/body weight, energy, and psychomotor activity, lack of concentration, feeling of guilt and worthlessness, and suicidal thoughts. For many patients diagnosed with BD, the depressive pole is more common and caused more suffering than the manic pole, leaving the patient exhausted. Studies show that depressive mood persists in 2/3 of the life in BD, even if the patient is under treatment (1–4).

DSM-5 contained specifiers for BD depressive episodes, these are showing birth-related onset (peripartum onset: onset during pregnancy or one month after birth) and seasonal correlation;, anxious/distress, mixed, fast-cycling, melancholic, atypical and mood-compatible or incompatible psychotic features (4).

Sub-threshold depressive symptoms in BD are resistant to treatment; this is the main and common cause of loss of function in patients. So, they must be handled carefully and treated rigorously (5–9).

In studies investigating the quality of life and psychosocial functionality in BD, it has been reported that depressive symptoms were the most influencing factor (10–12). Longer duration of episodes or early disorder onset with long duration of illness (12, 13) and neurocognitive decline were other features that affected this situation (14).

Diagnostic Difficulties

In BD, because the first episode of illness is depression, it may be difficult to differentiate from unipolar depressive disorder and diagnose BD, so the definitive diagnosis can be delayed. In the studies conducted on this topic, it has been determined that the correct diagnosis and therefore the treatment can be delayed for 6–8 years, and even longer if the disorder starts in adolescence (15–18). It is reported that 40% of the patients who were initially diagnosed with unipolar depression were later diagnosed with BD in the following years (19). This problem points out to the fact that the depressive episode is the most common pole in BD. It has been reported that, at the beginning of the disorder, episodes with anxious or mixed features also indicate future depressive episodes as much as depressive episodes do (20).

It may be difficult for patients with BD to recognize the symptoms of depression and seek help. Clinically valid hypomanic symptoms such as slightly elevated mood, increased libido and increased energycan be difficult to diagnose as they are not often considered by the patient as a reason for treatment seeking since these symptoms were generally egosyntonic. Therefore, at the onset of the disease, when the diagnosis cannot be made definitively, information should be obtained from a family member or close a friend (21).

Correspondence Address: Evrim Erten, Altınbaş Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, İstanbul, Turkey • **E-mail:** evrimerten@yahoo.com.tr
Received: 02.09.2020, **Accepted:** 21.05.2021, **Available Online Date:** 20.09.2021

The features that enable diagnosing bipolar depression and distinguishing it from unipolar depression are as follows: 1) presence of a family history of BD, hospitalization due to psychosis, psychiatric illness or disease history expressed as "nervous disorder" as expressed by the patient 2) early onset of illness, especially with depressive episode 3) cyclothymic temperament characteristics 4) four or more depressive episodes in a period of 10-years 5) depression with agitation, anger, insomnia, irritability, talkativeness or other "mixed" or hypomanic features or psychotic symptoms 6) clinical "worsening" and emergence of mixed symptoms that occurs after antidepressant (AD) treatment 7) suicidal thoughts and attempts 8) substance abuse 9) hypersomnia in a depressive state or presence of atypical features such as excessive daytime sleepiness, binge eating, psychomotor agitation.

As stated above, unipolar depressive disorder creates greatest confusion in the differential diagnosis of bipolar depressive episode. Patients are unlikely to remember their past hypomanic/manic episodes, and we rarely encounter them admitting those being pathological. In the acute depressive episode, the patient's insight and remembering may be slightly impaired due to memory problems such as concentration impairment and forgetfulness (22, 23).

From the very beginning, when diagnosing BD depressive episode, attention should be given to the coexistence of other psychiatric conditions such as anxiety disorders and substance use disorders. It should be kept in mind that this situation may lead to disability and increased suicide risk in young patients. When making a diagnosis in elderly patients, it should be noted that more medical diseases may occur together (20, 24).

Anxious Distress Features

The anxiety symptoms which are not included in the diagnostic criteria of bipolar or unipolar mood disorders were included in DSM-5 to draw the attention of clinicians to anxiety symptoms which may cause problems in monitoring and worsen the course and thus create changes in treatment planning. These symptom complexes implicit within the mood periods were included in the "those that could not be named otherwise" section of the DSM-IV in the past (25). Anxiety symptoms can often be seen during a depressive episode and may be predictors of more persistent depressive symptoms or an increased risk of suicidal thought (26, 27).

Mixed Features

In DSM-IV, the mixed episode was defined as the coexistence of manic and depressive episodes at the same time for at least 1 week, and this constituted a very rare condition, but accompanying mood episode symptoms from the opposite pole was a more frequent phenomenon. In DSM-5, mixed episodes were excluded from the diagnostic system, and mixed features of manic, hypomanic, and depressive mood were defined as specifiers. According to this, at least 3 or more symptoms from the opposite pole should be observed during the episode. For the manic episode, symptoms such as anxiety, guilt, negative thoughts about oneself, hopelessness, suicidal thoughts or behavior, anhedonia, fatigue or psychomotor slowing accompany the current picture (DSM-5). It has been reported that subthreshold hypomanic/manic features are observed in most of the patients in the depressive episode of BD, and this condition is associated with more severe depressive symptoms, high rate of substance use and cardiovascular disease (2, 28).

Bipolar Depression and Functioning

It is reported that depressive episodes comprise 72% of the disease duration for BD-I and 81% for BD-II in BD (28). Monitoring depression at such a high rate in BD is associated with loss of educational or occupational. 30–40% of the patients have prolonged periods of unemployment during the working years (3). In a review article in which the functionality of BD was discussed, it was reported that interpersonal functionality was determined by the increase in the number of depressive episodes rather than the number of manic episodes, and depressive weeks predicted the decrease in functionality in the general assessment of functionality scale. Social functioning especially improved when depressive episodes improved. It was also stated that sub-threshold depressive symptoms observed in the euthymic period caused a decrease in every aspect of functionality (9).

SUICIDE RISK IN BIPOLAR DEPRESSION

Depressive episode is important in terms of suicide risk in bipolar disorder. More than 70% of suicide attempts occur during this period. (24, 29) Depressive episodes with mixed characteristics have been reported to be riskier in terms of suicide attempt and death (30).

In the remission period of the disease, strategies should be determined for implementation in crisis periods together with the patient, and a written safety plan should be created regarding who to get support from. The most frequent way of suicide attempt in this patient group is through intoxication with drugs. Among these drugs, the most frequent causes of intoxication are opioids and benzodiazepines, which are taken at lethal levels, although their effectiveness in treatment is low (31). While the average annual suicide rate reported by WHO is 15.4/100,000 worldwide, this rate is reported as 20% for patients with BD (32, 33).

From a diagnostic point of view, the risk of suicide is equal for BD-I and BD-II, and the risk is the highest especially in those with mixed and psychotic features, followed by inpatients with major depression and then outpatients with moderate depressive disorder (33). The first days after leaving the hospital are period with greatest risk in terms of suicide attempts. During this period, the patient should be called for outpatient follow-up visits in a short time and should be monitored frequently and carefully (34, 35).

Overall Assessment in Treatment of Bipolar Depression

The primary treatment goal in BD should be to ensure the recovery of the patient, to maintain it, to prevent recurrence, and to restore functionality completely. Long-term maintenance therapy should also be considered while choosing the treatment of the acute period. A safe drug should be chosen for long-term treatment and acute-term efficacy, and attention should be paid to side effects. (36)

After establishing the diagnosis of bipolar depression, the first evaluation that should be done is clinical psychiatric examination. During this period, the severity of depressive symptoms, presence of psychotic symptoms, self-harm or suicidal thoughts and suicidal intent should be investigated. It is also necessary to determine the past treatment compliance, to assess the appropriateness of social support, and to specify the psychosocial loss of functionality.

Necessary laboratory examinations are as follows; complete blood count, fasting blood glucose (FBG), lipid profile (TG, VLDL, HDL, LDL), liver, kidney and thyroid function tests, electrolytes including calcium, ECG in patients over 40 years of age, pregnancy test for women in reproductive age and urinary toxicology tests if substance use disorder is suspected. Before the treatment is initiated, the symptoms related to alcohol/substance use, the symptoms that may arise due to the other drugs used by the patient and other medical conditions should be differentiated from depression. A detailed history of previous mood episodes, treatments found to be beneficial in these periods and the side effects associated with these medicaitons should be recorded. It should be investigated whether the drug was discontinued before the depressive episode and whether the symptoms occurred due to this discontinuation. According to the results of the examination, the most appropriate and safe treatment choice for the patient should be determined (37–40).

Acute Treatment of BD Depressive Episode

The number of studies conducted on the treatment of bipolar depression is limited, and the information on this subject is based on the data on this group from previous studies or on information obtained from unipolar depression treatment (37–40). This limited information is predominantly valid for BD-I, but treatment for BD-II depressive episode is uncertain. The use of ADs for BD-II poses a risk for hypomania, mixed episodes or rapid cycling. Again, unlike unipolar depression, there are negative results related to cognitive behavioral therapies (CBT) in bipolar depression (37–40).

While in CANMAT (Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders guidelines) (2018) for BD depressive period, quetiapine, lurasidone + lithium/valproic acid, Lithium, lamotrigine, lurasidone + lamotrigine is recommended (38); in BAP (British Association for Psychopharmacology guidelines)-2016) for acute treatment of BD depressive episode, quetiapine, lurasidone or olanzapine is recommended in the first place (39). On the other hand, at NIH (National Institute for Health and Care Excellence guidelines-2018) olanzapine + fluoxetine or quetiapine is recommended, but for WFSBP (World Federation of Societies of Biological Psychiatry-2010) only quetiapine is in the first place (37, 41). In RANZCP (the Royal Australian and New Zealand College of Psychiatrists-2015) quetiapine, lurasidone, olanzapine, lithium, lamotrigine, and valproic acid come first in treatment of BD depressive episode (40). As a result of the analysis of double-blind randomized controlled trials, it has been reported that quetiapine is more effective in the treatment of distress/anxiety symptoms in the depressive period compared to placebo, and the combination of olanzapine + fluoxetine has been reported as an effective treatment (42, 43).

In another analysis study, it was reported that lurasidone was effective in anxiety symptoms as well as depressive symptoms in unipolar depression (44). Valproic acid, risperidone and lamotrigine appear to have limited anxiety-relieving effects (45).

It has been reported that a reliable treatment for BD depressive episode, which has mixed features, has not been clearly effective yet, and atypical APs should be used in the initial phase of treatment in these patients (46). Asenapine, lurasidone and the combination of olanzapine + fluoxetine is effective in this group of patients (47). The ISBD task group does not recommend the use of ADs in patients with BD depressive episode (48).

Acute period treatment of BD depressive episode according to treatment algorithms is shown in Table 1.

Medications used in Acute Treatment of BD Depressive Episode

Lithium

In the treatment of BD, lithium has been an essential treatment for many years. It has been the first-line treatment in some treatment algorithms (38, 39), though, it was not actually tested in BD in the depressive period. In a study where quetiapine was investigated as a primary drug, it was reported that lithium did not make a difference in treatment compared to placebo, but that in this study, the mean lithium levels were 0.65 mEq/l, and 35% of the patients had a lower levels. In fact, lithium was effective in preventing depressive episodes in higher maintenance doses (0.8–1.2 mEq/l) (49).

In addition, it is known that lithium has a protective effect in preventing the recurrence of BD depressive episode and decreasing the occurrence of hypomania/manic episode and mixed episode (39, 50–52), and reduces the risk of suicide (53, 54).

Anticonvulsants

Lamotrigine (LMT): Lamotrigine's effectiveness in acute BD depressive episode has not been determined. In a placebo comparative study, it was reported to be beneficial in depressive episodes, and a similar result was found in another study (55). Lamotrigine has FDA (US Food and Drug Administration: American Food and Drug Administration) approval for the prevention of the recurrence of the depressive episode and long-term preventive treatment of BD (20, 56). In the CEQUEL study, Lamotrigine was added to the treatment of BD patients who received quetiapine, and compared with placebo; it was reported to have significant benefits

TREATMENT OF BIPOLAR DEPRESSION

CANMAT and ISBD 2018: Treatment Guidelines for depressive episode of bipolar disorder
- First line: (a) quetiapine; (b) lurasidone + lithium/valproate; (c) lithium; (d) lamotrigine ; (e) lurasidone; (e) lamotrigine (add-on.) - Second line: (a) valproate; (b) SSRIs/bupropion + antimanic / antipsychotic; (c) ECT; (d) cariprazine; (e) olanzapine + fluoxetine - Third line: (in alphabetical order as an add on treatment) (a) aripiprazole ;(b) armodafinil ;(c) asenapine ;(d) carbamazepine; (e) eicosapentaenoic acid (EPA) ;(f) ketamine (IV) ; (g) light therapy ± total sleep deprivation ; (h) levothyroxine (i) modafinil (add-on); (j) N-acetylcysteine ; (k) olanzapine; (l) pramipexol (m) repetitive transmagnetic stimulation (rTMS); (n) SNRI/MAOI
British Association for Psychopharmacology: 2016
- For patients who didn't have a long term preventive medication: (a) quetiapine; (b) lurasidone; (c) olanzapine - Lamotrigine + mood stabilizer/ antipsychotic to prevent new manic episodes - If an antidepressant treatment was considered; an antimanic / antipsychotic drug could be given especially in patients who had a manic episode. Olanzapine + fluoxetine combination can be eligible. - If the depressive symptoms are not severe lithium should be preferred. - ECT should be considered in treatment resistant, suicidal or pregnant patients and for the patients who were not eating/drinking . - Cognitive behavioral therapy, family-focused therapy/interpersonal rhythm therapy could be added to treatment.
International College of Neuro-Psychopharmacology-CINP) Adult BPD Guideline : 2017
- First step: quetiapine/ lurasidone.. - Second step:(a) olanzapine ± fluoxetine (b) mood stabilizer + lurasidone, modafinil / Pramipexol; (c) lithium+ lamotrigine; (d) escitalopram or fluoxetine can be added to existing treatment - Third step: (a)valproate, aripiprazole, imipramine, phenelzine, carbamazepine, lamotrigine monotherapy (b) lithium+ L-sulpiride - Fourth step: (a) tranylcypromine / lithium monotherapy (b) venlafaxine + antimanic; (c) armodafinil or IV ketamine+ mood stabilizer (d) lithium + fluoxetine / lamotrigine; (e) mood stabilizer + l-thyroxine (L-T4); (f) lithium + oxcarbazepine - Fifth step: ECT or different drug combinations according to clinician or patient's experiences

on depressive symptoms in the early period and improvement in 1-year monitoring (57). There is a study reporting that the addition of lamotrigine to the lithium is effective in the treatment of BD. It should be kept in mind that at the beginning of the treatment, lamotrigine dose should be titrated slowly in order to reduce the risk of dermatological side effects, and it is recommended to reduce the LMT dose by 50% when used with Valproic acid (58).

Valproic Acid: Although it was reported to be effective in the treatment of acute BD depressive episode in 4 small sample studies, it was not approved by the FDA for the acute or long-term treatment of BD. In addition, caution should be exercised when used in female patients of reproductive age, due to the risk of teratogenic risk in the newborn (59).

Antidepressants

The use of antidepressants in the treatment of depressive episodes and the fact that the clinical findings of the BD depressive episode are relatively similar to the characteristics of the unipolar depressive episode led to the use of AD alone in the treatment of BD depressive episodes for years (60). However, there has been an opinion over time that the use of AD treatment in the depressive period of BD may cause a possible dangerous agitation or mania, especially in BD-I (61, 62). It has been reported that such risks are observed more frequently in patients with DME (depression-mania-euphoria) course for BD in long-term monitoring compared to patients with MDE (mania-depression-euphoria) course (63). However, it may be difficult to distinguish between spontaneous and AD-related manic shift in BD (13.8% [12.2–15.3] versus 15.3% [14.5–16.1]); in this sense, the rate of manic shifts appear to be similar (64).

Although it has been thought that manic shifts can be avoided with the addition of mood stabilizers or antipsychotic drugs to ADs in treatment, randomized comparative studies conducted within this framework are limited (60, 64). It has also been reported that short-term use of ADs alone or in combination with a mood stabilizer (MS), has little risk compared to placebo in terms of the risk of new manic episodes (63). On the other hand, it was stated that the risk of deviation in BD is 2.8 times higher in 9-month monitoring in cases where MS was not used but AD is added to the treatment (65). All these constitute a common clinical opinion that the use of ADs in BD should be with extreme caution, and for a short time if possible. Dose increases should be slow. It is appropriate to closely monitor for hypomania, and ADs should be used together with an effective mood stabilizer. In BD-I, it is necessary to avoid or very carefully use the tricyclic antidepressants (TCA) and serotonin-noradrenaline reuptake inhibitors (Serotonin Norepinephrine Reuptake Inhibitor-SNRI), especially in patients with a history of manic episode or rapid cycling without AD use and with mixed characteristics (64, 66). In treatment guidelines, addition of AD treatment (serotonin reuptake inhibitor-SSRI or bupropion) to Lithium/Valproic acid or AAP is recommended in the second line under additive therapy (38). A meta-analysis supports this notion despite reporting a low potency (65, 66). If it is necessary to use it, patients and their relatives should be educated about mood changes and rapid cycling, and AD treatment should be discontinued when such a situation occurs. As a result, AD monotherapy is not recommended in the treatment of BD (48).

Atypical Antipsychotics (AAP)

Among the AAPs, cariprazine, lurasidone, olanzapine + fluoxetine and quetiapine are drugs approved by the FDA in the treatment of acute phase of depressive episodes in BD (53, 67, 68). Among these drugs, only quetiapine has been shown to be superior to placebo in many studies over the years. FDA accepted 300 mg/day as the treatment dose although similar results were obtained for 300 mg/day and 600 mg/day (69). Olanzapine-fluoxetine combination was superior to placebo, but olanzapine alone was found less effective (70). Both olanzapine and quetiapine have antimanic effects and the risk of manic switch was lower than placebo (68). Further studies are required to understand the long-term protective effects of these drugs, which have moderate effects in the treatment of acute BD depressive episode. Effective doses of antipsychotics may have side effects such as excessive sedation and akathisia (71).

Also, other components of metabolic syndrome such as weight gain, type-2 DM, hyperlipidemia and hypertension should be considered during monitoring (20, 72). Such side effects limit the possible role of AAPs in long-term treatment of BD depressive episode. To sum up, cariprazine, lurasidone, quetiapine and olanzapine-fluoxetine combination are effective drugs with some risks in the treatment of BD depressive episode (73).

Aripiprazole monotherapy (5–30 mg/day) was not superior to placebo in two similarly patterned, 8-week, randomized, double-blind placebo-controlled studies (74).

Brexpiprazole: It is a serotonin and dopamine receptor modulator with sub-nanomolar potent antagonist properties for serotonin 5-HT2A and α1A adrenergic receptors and a partial agonist for serotonin 5-HT1A and dopamine D2 receptors. Used as 4 mg/day in an 8-week open-label study, it is reported that Brexpiprazole has positive effect. Again, in this study, it is reported that it provides an increase in quality of life and improvement in cognitive functions at the end of 8 weeks (75).

Other Treatments

Modafinil: Modafinil inhibits low level of dopamine transport. In a 6-week placebo-controlled study conducted by adding the mood stabilizer + AD combination, a significant response and improvement was observed (76).

Pramipexole: It is a D2/D3 receptor agonist, used in two small-scale, 6-week randomized controlled studies, in the treatment of BD depressive episode with its addition to mood stabilizers, and a better response was obtained compared to placebo (77, 78).

Ketamine: It has an antagonist effect on N-methyl-D-aspartate (NMDA) receptors in glutamate receptors. In addition, ketamine and its active S-enantiomer (esketamine) inhibit the transport of noradrenaline and serotonin, which are effective in rapidly relieving depressive symptoms and eliminating suicidal thoughts. It has been reported to have an effect on patients with BD depressive episode, but its effect on suicidal behavior in this patient group is still not fully determined (79). There are concerns that adverse clinical responses may occur after cessation of racemic or s-ketamine therapy. The necessity of administering ketamine only in hospital conditions and with anesthesiology creates difficulties in its use, so studies on its intranasal administration are ongoing. Side effects include dizziness, blurred vision, restlessness, nausea or vomiting, and headache. Side effects are generally reported to be transient and of moderate intensity. It was reported that repetitive intravenous use may lead to toxic effects, and result in temporary psychomimetic effects that may increase blood pressure, but permanent psychotic symptoms or mood swings are not expected (80, 81).

Riluzole: It stops glutamate release, facilitates glutamate reuptake and AMPA (α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid) exchange. It blocks voltage-gated channels connected to Na. In an open 8-week study, lithium augmentation with riluzole was found to be effective in 14 patients with BD with moderate depression, but riluzole monotherapy was stopped in an 8-week placebo comparative study because of ineffectiveness (82, 83).

N-acetyl cysteine: It is reported to be effective in reducing oxidative stress and inflammation by increasing glutathione levels in the brain. In a 24-week multicenter randomized controlled study, significant improvement was observed in the Montgomery and Asberg Depression Rating Scale (MADRS) scores during the maintenance period compared to placebo when added to treatment as usual (38, 84).

Upon the observation that BD is associated with many medical conditions, it has been suggested that it is a multisystem anti-inflammatory disease and anti-inflammatory drugs have been used as an addition in the treatment. Among these, nonsteroidal anti-inflammatory drugs, omega-3 unsaturated fatty acids, N-acetyl cysteine and pioglitazone have been suggested to have significant antidepressant effects (38, 85).

Celecoxib: Celecoxib, a cyclooxygenase-2 inhibitor, was added to escitalopram treatment in an 8-week placebo-controlled study involving patients in the depressive episode of BD, and responded well compared to placebo (86).

T3: Thyroid hormones affect the function of serotonin, catecholamine and dopamine systems in brain. When added to treatment in the BD's depressive subgroup, a significant decrease in the severity of depression was observed after 1 week compared to the control group in a comparative study (87).

Electroconvulsive Therapy (ECT): It has been reported that ECT is life-saving in the depressive period of BD, especially in cases with a risk of suicide in treatment-resistant cases, and the antidepressant response after ECT increases to 68% (88). If there is treatment resistance in the acute period, and if there is high suicide risk, psychotic symptoms, severe and retarded depression or refusal to eat or drink, ECT can be used (39).

Other methods such as transmagnetic stimulation, vagal nerve stimulation and deep brain stimulation are currently being investigated in treatment-resistant depression.

Among other non-pharmacological treatments, intensive-light therapy and sleep deprivation are among the possible candidates to be tested in the bipolar depression (89). Vagal-nerve stimulation is recommended by the FDA in treatment-resistant cases of both unipolar and bipolar depression, although there is some risk of manic shift (90).

Psychotherapy is generally recommended for the depressive episode as augmentation treatment. These psychotherapies include cognitive behavioral therapies, family-oriented psychotherapies, and interpersonal social rhythm therapy (39). The main limitation in these analyses is that the results could not be generalized to the entire BD sample because the patients who applied to long-term treatments voluntarily causes selection bias for these studies.

Maintenance Treatment of Bipolar Disorder Depressive Episode

When choosing a drug in the maintenance phase, patient and caregivers should also take role in the decision. Meanwhile, response to the previous and current medications, side effects, predominant polarity and clinical features that prognostic importance should be taken into consideration. It is recommended that lithium should be chosen primarily in patients with euphoric mania without depressive symptoms, patients with a course of illness in the form of Mania-Depression-Euphoria, and if there are smaller number of mood episodes, a family history of BD or good response to lithium (91, 92).

Valproate is recommended in classic mania and mania with dysphoric features, for those with multiple mood episodes, irritable, dysphoric or mixed characteristics, and/or those with a history of accompanying substance use and head trauma (92, 93). It should be used with caution for women in reproductive age because of teratogenic side effects.

In the maintenance period, it is generally recommended to continue treatment with the drug that was effective in the previous mood period, even if it was not included in the guidelines as first line (40, 41). If the drug is among the first-line options such as lithium, quetiapine or their dual combination, it is recommended to continue or choose according to the previous response/unresponsiveness, whichever mood is dominant.

In other guidelines, treatment protocols that include the maintenance period as long-term therapy are mentioned instead of maintenance (41). It is stated that the aim of treatment should be preventing new mood episodes and maintaining continuous instead of intermittent treatment. As a result of randomized controlled trials, it has been reported that the long-acting intramuscular form of lithium, quetiapine, risperidone and valproate prevent the emergence of the manic episodes at different levels of efficacy. Lamotrigine, lithium and quetiapine were effective in preventing the emergence of depressive episodes. Similar recommendation has been made for lurasidone recently. One of the strong evidences about the treatments in this period is that lithium is protective during the maintenance period even in patients who do not respond adequately in the acute phase. Most of these studies were conducted with BD-I patients. Short-term addition of dopamine antagonists/partial agonists is recommended in the event of an acute stressor, insomnia or anxiety.

Double blind controlled trials, naturalistic studies and reports of hospitalization records recommend to choose lithium as the initial treatment. The order of preference is lithium >valproate >olanzapine >lamotrigine >quetiapine, respectively. Again, lithium has been found more effective than other drugs with its suicide preventive effect in the treatment of both manic, depressive and mixed episodes. For the maintenance period, a serum level of 0.6–0.8 mmol/L is recommended.

In naturalistic follow-up studies, it is stated that valproate can also be used in long-term treatment as a mood stabilizer. It is recommended that lamotrigine should be used together with an agent with antimanic properties in the maintenance treatment of BD-I. If a patient does not respond to monotherapy and sub-threshold depressive symptoms or mood episodes reappear, the long-term scombination treatments are required. If depressive episodes are prominent, combination of lithium, lamotrigine, quetiapine, lurasidone or olanzapine is recommended. It is also among the recommendations that antidepressants should be tapered and discontinued at least 12 weeks after the symptoms of full recovery are seen, but if depressive symptoms occur after discontinuation, a longer-term treatment is also recommended (40, 41).

Maintenance ECT can be considered in patients who have responded well to ECT in the acute period but have not responded to oral therapy (41).

Another intervention that should be planned during the maintenance period is the inclusion of psychoeducation. Psychoeducation is, in a broad sense, providing information to the patient and their family about the nature of the disease, its treatment and coping strategies with the disease. In the existing psychoeducation models, there are elements such as the awareness of the early symptoms of depression and manic period, managing ongoing stressful situations, developing problem-solving skills, preventing denial of the disease, ensuring compliance with treatment, implementation of the things that are required for a regular and healthy life (e.g. regulating the sleep-wake cycle, reduction of alcohol-substance use, caffeine or other stimulants). The main goal is developing coping skills that are personalized and comprehensive. Psychoeducation can

be planned face to face as individual or group sessions. Recently, online applications have also been involved in treatment (40).

BIPOLAR II DISORDER (BD-II) – DEPRESSIVE EPISODE

BD-II is different from BD-I, and is diagnosed by the presence of one or more hypomania, one or more depressive episodes and the absence of any manic episodes. The DSM-5 diagnostic criteria for hypomania are similar to those for mania, and these symptoms are that the individual behaves differently from their personal characteristics, are completely noticed by others, and continue for at least 4 consecutive days. In contrast to mania, a significant impairment in functionality and hospitalization is not present and does not contain psychotic elements. Mixed features with DSM-5 are also added as specifiers. The patients that are diagnosed with BD-II are generally followed up in the same principles, but in a group of patients, transition to BD-I can be seen in the early period of the disease (94).

Although hypomania is clinically less severe than mania, the economic burden can be 4 times higher in BD-II than in BD-I (95). The reason for this is that symptomatic period in BD-II is no less than in BD-I patients. It is known that mood symptoms are generally seen as depressive episodes, and the ratio of depressive episode to hypomanic period has been reported to be 39:1 (96). The rates of suicide attempt and completed suicide are similar in BD-II and BD-I, and one-third of patients with BD-II attempt suicide during their illness, and one in twenty-five patients die as a result of suicide. Depressive episodes are often severe in BD; it is a process that progresses with cognitive impairment, decreases the psychomotor activity of the patient and can lead to death as a result of cardiovascular disease and suicide. Although hypomanic periods are pleasant for some patients, dysphoric features accompany the clinical picture in two-thirds of women and 40% of men, and patients feel anxious, agitated, irritable and under pressure and do not like it (97).

The treatment of BD-II was studied less than BD-I, possibly due to the longer duration and less severe course of the disease. In addition, in many studies, BD-II and BD-I patients were included in the study together, and the results were not stratified for the two clinical groups. This creates difficulty in determining whether there is a difference in clinical understanding between the two disorders in terms of response to treatment. Therefore, many studies report that BD-II and BD-I disorders respond to mood stabilizers and antipsychotics similarly, but there are also studies reporting that this is not the case (98).

For example, if half of the patient group in the study did not consist of BD-II patients, the result of the study was not stated as an expert opinion for BD-II patients (38). Methodologically, the lack of clinical studies with large samples raises controversial issues for evidence-based treatment guidelines. For BD-II patients, there are fewer treatment recommendations at a high level of evidence for first-line treatments than for BD-I patients. For this reason, the information on this subject is mostly based on clinical experience, and the data in some existing studies should be compiled in more detail. And again, more efficient studies are required for all periods of BD-II (40).

Acute Treatment of the BD-II Depressive Episode

The first recommended drug in the treatment of BD-II depressive episode is quetiapine. Combining five similar studies, it was better than placebo and equally effective in BD-I and BD-II during depressive episodes. Although it was stated in these studies that it is less effective in patients with BD-II, the number of patients with BD-II was quite low in these studies, which consequently decreased the statistical power (99).

In BD-II patients in the depressive episode, lithium (0.8–1.2 mEq/L) is the second-line recommendation. Lithium was ineffective in a placebo-controlled study in the depressive episode of BD-II patients (100, 101). The reason why lithium fell to the second rank was that lithium was reported as effective as sertraline in a 16-week double-blind study, and similar to lamotrigine in a 6-week lamotrigine study. These studies were not placebo-controlled. (96, 102, 103)

In a 12-week randomized controlled study, lithium was less effective than venlafaxine (104). In a meta-analysis, mood elevations due to AD were examined in BD-I, BD-II and unipolar patients, founding that this rate was low or remained at the level of hypomania in BD-II (61). The use of AD was restricted to sertraline, bupropion, and venlafaxine because there are no studies on BD-II acute depressive episode of other ADs. Fluoxetine ranks lower. The ISBD task group reports that ADs can be used in monotherapy for BD-II, but if there is a rapid cycling or manic shift in the history, they should be used in combination with mood stabilizers (48).

Lamotrigine is also recommended for BD-II patients as the second-line option in the depressive period. While it was found ineffective in a meta-analysis study, it was effective as lithium at higher doses (300 mg/day) in longer period (16 weeks) in BD-II patients in a single-blind randomized controlled study (100). Two large randomized controlled trials and a 12-week open-label study reported good response when lamotrigine was added to the treatment, but the patients in these studies included patients with all mood disorders, and patients with BD-I are not treated separately (49, 58).

ECT is recommended in the second line especially in treatment-resistant patients and in cases where rapid response is required (105).

Valproate monotherapy is recommended in the third line, and fluoxetine, tranylcypromine or ziprasidone are recommended in patients with depression (38). Again, it is reported that agomelatine, bupropion, N-acetylcysteine, pramipexole and thyroid hormone can be added as in BD-I. In other treatment guidelines, a separate section has not been allocated to BD-II, and the treatments for BD-II– are described in the depressive episode (37, 40, 41).

Maintenance Treatment of BD-II Depressive Period

As in BD-I, the aim of maintenance therapy should be to prevent recurrence of the disorder, to cure sub-threshold symptoms and to increase quality of life. For this period, quetiapine is recommended as the first and lamotrigine and lithium as the second options. In two separate 52-week maintenance studies conducted with quetiapine, BD-II patients who recovered with quetiapine in the depressive period were divided into two groups as quetiapine monotherapy or placebo. Time to recurrence of any mood or depressive episode was significantly longer in patients who remained on quetiapine monotherapy. Quetiapine is effective in BD-II as well as BD-I; it has been reported that there is a 42%, 48% depression and a 30% risk of developing a manic episode in the monitoring for the recurrence of any mood episode (in terms of the risk of developing mania, hypomania or a new depressive episode), respectively (106). In a study with a 6-month follow-up period, lithium or quetiapine were added to the current treatment of the patients, respectively, and both drugs were significantly effective in preventing relapse (107).

Long-term naturalistic follow-up study results provided some evidence for lithium. In a 6-year study, in any patient with a diagnosis of BD-I and BD-II (39% of them were patients with a diagnosis of BD-II), lithium was found to reduce the development of hypomania/mania by 61% and the occurrence of depression by 53% compared to the period before using lithium (108).

In a six-month, randomized placebo-controlled study, lamotrigine was used in patients diagnosed with BD-I and BD-II with rapid cycling, and

post hoc analyses reported that the results of the patients with BD-II were more stable and that a new mood episode did not develop, but lamotrigine was similar to placebo in BDI-I (109).

In a 6-month randomized controlled study, the recurrence rate of depression was lower in those treated with venlafaxine for those who are responders to venlafaxine or lithium in the acute phase of BD-II without hypomanic shift. Again, it was reported that the response to venlafaxine was more permanent and long lasting for both groups. No hypomanic episode was observed in the follow-up in both groups (110).

In a 50-week randomized controlled study with fluoxetine, the duration of of period until the next depression was significantly longer in fluoxetine than lithium or placebo (111). Again, in a small study comparing placebo for 6 months, it was reported that the recurrence rate was lower with fluoxetine compared to placebo (112).

Valproate, carbamazepine, escitalopram and other antidepressants and risperidone are among the third-line options (38).

CONCLUSION

The first important aspect of the BD depressive episode is that patients should be diagnosed accurately in the early period, and their treatment should be done carefully. In most of the patients, the first episode is depression, so patients receive a diagnosis of unipolar disorder and they are treated incorrectly with AD monotherapy (113).

Many patients with BD can be diagnosed with any kind of personality disorder, and these patients often receive psychotherapy and AD treatment inappropriately for a long time. Another problem is that positive treatment response is usually achieved at any stage of the treatment, often with 2–3 kinds of medications, but in a sufficient number of patients' complete recovery is not achieved with none of these medications in long-term. Considering the longitudinal disorder process, with full blown episodes constituting a small duration of the disorder, sub-threshold symptoms that do not constitute a complete clinical syndrome cause significant disability and burden (1, 114). Many authors state that treatments usually reduce symptoms, but fail to achieve goals such as complete elimination of disability and complete recovery (115, 116). This is especially true for the depressive episode of BD. The treatment-resistant mental processes here create a high risk of suicide and causes long-term loss in functioning (116).

The short-term "safe" use of AD treatments is still controversial and should be avoided when dysphoric or mixed states are present, as there is still insufficient data on their long-term use. In BD depressive episode, AAPs treatment is effective in acute treatment with quick response, but lithium and lamotrigine have not been adequately investigated in short-term treatment, although the longer-term protective effects of them are well known. There is little evidence for the short- or long-term efficacy of other anticonvulsants in the treatment of bipolar depression. Considering all these, we can state that BD is less profoundly studied than unipolar disorder, and the place of standard ADs in the treatment of BD is controversial in terms of reliability and tolerability. In addition, almost all treatments used in the depressive episode of BD have metabolic or neurological side effects (20). For these reasons, new agents with proven long-term protective effects that also reduce morbidity and mortality and strategies for differentiating bipolar from unipolar depression are needed.

Peer-review: Externally peer-reviewed

Conflict of Interest: No.

Financial Disclosure: This article has not received any financial support or assistance.

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