

REVIEW

Acute and Long Term Treatment of Manic Episodes in Bipolar Disorder

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ABSTRACT

Bipolar disorder is a disabling psychiatric disorder which causes premature death and loss of quality of life. Despite the developments, novel treatments are partially effective and insufficient responses to treatment may cause loss of quality of life. Contemporary approaches to treatment planning involve taking the current symptoms and the personal treatment history of the patient into account and tailoring them for the treatment of each patient, i.e. individualized treatment. In this article, effects and side effects of antipsychotics, mood stabilizers and sedative hypnotic medications are reviewed and presented briefly for clinicians. Although novel developments have been observed in

the literature about mixed states and psychotic symptoms, evidence-based options are still limited. Efficacy of mood stabilizers may be prolonged and additional medications may also be needed frequently in patients treated with mood stabilizers. Antipsychotics may cause several side effects and cannot be maintained for a long time in some of those patients. These factors may limit the use of mood stabilizers or antipsychotics. Therefore, the experience of the clinician and personal history of the patient still have importance in the procedure.

Keywords: Mania, bipolar disorder, treatment resistance

Cite this article as: Atagün Mİ, Oral T. Acute and Long Term Treatment of Manic Episodes in Bipolar Disorder. Arch Neuropsychiatry 2021; 58 (Suppl 1): S24-S30.

INTRODUCTION

Bipolar disorder (BD) is a psychiatric disorder that presents with manic and depressive episodes. The mood episodes appear as random and unpredictable episodes. The frequency and course of manic and depressive episodes may vary in each case and be determined by environmental factors as well as patient susceptibility. A study from the United States reports that the lifetime prevalence of bipolar disorder is 2.4% and the incidence rate of new cases in a year is 1.4% (1). The bipolar spectrum disorders are BD type 1 (BD-1), type 2 (BD-2), cyclothymia and not otherwise specified BD (2). Although depressive symptoms and episodes are more common, manic episodes are required for the diagnosis. According to the latest edition of the American Psychiatric Association's (APA) *The Diagnostic and Statistical Manual of Mental Disorders* (DSM 5), during manic episodes, patients exhibit elevated or irritable mood, hyperactivity, increased speed of speech or need to talk, flight of ideas, inflated self-esteem, decreased need for sleep, distractibility, and interest in risky activities. Unless treated, a manic episode can last around 4-13 months. The frequency of symptoms in decreasing order are increase in the speed of speech (98%), increase in the urge to talk (89%), increase in activity (87%), decrease in the need for sleep (81%), increase in sexual activity (57%), and overspending (55%) (3). Despite the fact that it appears in a variety of sources and is frequently discussed in clinical interviews, "overspending" is not included among the diagnostic criteria.

In terms of diagnostic criteria, hypomania is defined as a version whereby mania symptoms affect social and professional functionality less (2). Moreover, another difference between a manic episode and a hypomanic one according to the DSM-5 diagnostic criteria is their duration. Duration of 1 week for mania and 4 days for hypomania are required (in both

diagnoses, if there is treatment, duration criteria are annulled). However, in cases where hypomania lasts long or relapses occur frequently, functionality might also be adversely affected even in hypomania. There is a change in the definition of hypomania between DSM-IV and DSM 5 whereby increase in activity and energy has become one of the two main symptoms. The note that hypomanic episodes triggered by medication and treatment are adequate for a bipolar disorder diagnosis was also added. Both hypomanic and manic episodes can be seen in BD-1. However, in BD-2 patients, no manic episodes are observed, only depressive and hypomanic episodes are present. It was reported that only manic episodes (unipolar mania) were observed in a small group of BD-1 patients (4, 5). Manic episodes with mild cognitive and mood symptoms, as well as those with serious behavioural organizational disturbances may be seen in the clinical context. In case of mild symptoms, such as the hypomanic episodes, an increase in productivity is possible. In the case that the disorder becomes uncontrollable during the episode of mania, it may lead to situations that pose danger to the patient or the public. Cases that have the potential to engender serious situations in particular, such as self-harming behaviour, sexual behaviour that is outside the person's usual life experience, random and unnecessary spending of money, over activity and risky behaviour tend to worry the people in the patient's life and the clinicians. In order to be prepared for such risky situations, patients, their relatives and physicians tend to take precautions against manic episodes. Therefore, it could be said that the choice of treatment during the symptom-free periods of BD is aimed more towards being preventative against manic episodes (6). However, in such relatively heavy treatment regimens, treatment compliance tends to be proportionally low. Therefore, defining treatment targets from the very beginning gains

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Received: 03.09.2020, **Accepted:** 26.05.2021, **Available Online Date:** 20.09.2021

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precedence. Treatment targets include the treatment of acute manic and depressive episodes, prevention of switches to the opposite pole during acute treatment, prevention of relapses during periods of remission, and prevention of suicidal behaviours and behaviours that have the potential to effect social adaptation. Since such features as lability in mood, mixed symptoms like those in dysphoric mania, rapid cycling course, history of swings to the other pole, number of past episodes, presence or absence of psychotic symptoms, history of alcohol or drug use, and psychiatric or physical dual diagnoses can also be influential in treatment (7, 8), it is important that these factors should also be assessed.

Terms such as response to treatment, resistance to treatment, improvement and recovery are frequently used expressions regarding treatment (9, 10). Young Mania Rating Scale (YMRS), the Turkish translation of which is clinically determined to be valid and reliable, is widely used in the assessment of the severity of manic episodes (11). In this scale, the response to treatment within an 8-10 week treatment process is evaluated with grades of scores such as “below 25%, 25–49%, 50–74%, 75–100% decrease.” During the treatment process, as the YMRS scores decrease, scores from the depression scales should also be tracked. However, at the end of a treatment period of 8-10 weeks, less than 25% or no decrease on YMRS scores is considered resistance to treatment. Improvement is determined if the total scale score remains 5 and below. Total disappearance of symptoms or the presence of maximum two symptoms for at least two weeks after improvement is considered recovery (10, 14).

During treatment, cooperativeness of the patient should be evaluated first, in terms of attitude and insight. Moreover, an assessment is necessary for risky cases and situations that require emergency intervention, such as rejection of treatment, inclination to violence, and impulsivity and uncontrolled behaviours. In risky cases or lack of patient cooperation, hospitalization and implementation of treatments that produce rapid results are necessary. Treatment should be designed after precautions. For instance, if antidepressant medication is being used at the time, they should be stopped; alcohol/drug use should be prevented; and the thyroid levels of patients who take thyroid hormones should be checked. It is thought that excessive dopaminergic neurotransmission contributes to the pathophysiology of manic episodes. This idea results from observations that manic episodes improve with the regulation of D2/D3 receptor activities and that depressive mood swings are due to the excessive blockade of the dopaminergic receptors (12). However, in later studies, no cases of hyperdopaminergic/hypodopaminergic states in dopaminergic cells or in the intrinsic activities of the dopaminergic cells have been observed. In the treatment of the manic episodes of bipolar disorder, mood stabilizers (lithium, valproic acid, carbamazepine), antipsychotics, sedative-hypnotics, therapeutic neuromodulation treatments such as electroconvulsive therapy (ECT), vagal neural stimulation, transcranial magnetic stimulation (TMS), psychosocial interventions, and psychotherapeutic approaches are used. These treatments and their uses will be discussed in the following sections of the article (9, 10).

MOOD STABILIZERS IN THE TREATMENT OF ACUTE MANIC EPISODES

Mood stabilizers (MS) can be used in the treatment of acute mania as monotherapy or as part of a combination treatment. U.S. Food and Drug Administration (FDA) has approved the use of lithium and valproate for acute mania indication. Lithium (Li) among the mood stabilizers and carbamazepine and valproate among the anticonvulsants are medications that can be used in the treatment of mania. However, lamotrigine, topiramate, gabapentin and oxcarbazepine, are known to be ineffective in prophylaxis and the treatment of manic episodes (13). Among these, only lamotrigine is known to have prophylactic effect on depressive episodes.

In order to avoid side effects and drug interactions, mood stabilizers are recommended to be used as monotherapy as much as possible. However, although they have high prophylactic effect against manic episodes, their acute impact is delayed. Consequently, in cases where they are used as monotherapy, the acute manic episode may continue for a period of time and risky situations may arise. As an exception, valproate may have an advantage with its quicker effect time due to its rapid titration and maximum tolerated dosage. Therefore, mood stabilizers are not recommended to be used as monotherapy in the treatment of acute mania in particularly risky and urgently dangerous situations (14, 15). Yet, they may be used as monotherapy in the treatment of mild or moderate manic episodes provided that the patient is observed closely. In cases of psychotic symptoms, risky behaviours, and inadequate compliance to treatment, mood stabilizers should be used with antipsychotics. However, they are a better option than antipsychotics in terms of reducing the risk of depression following mania.

Lithium stands out as the most commonly used drug in this group. In all the studies that lithium monotherapy was compared against placebo, it outperformed the placebo in the treatment of acute mania (16). When combined with antipsychotics, it speeds up treatment and renders controlling mania easier. However, in the case of combined treatment, due to the notable drop in the patients' continuation of treatment in the long term, it is recommended to stop antipsychotics as soon as possible and continue lithium on its own (17). Since there may be a significant increase in side effects when lithium is used with first-generation antipsychotics, particularly haloperidol, their combined use is not recommended. If it is being used as monotherapy and symptoms such as decreased need for sleep, over-activity, anxiety and agitation develop, benzodiazepines can be used for these symptoms. If the patient seems to benefit, they can be used regularly for 7-10 days (18). Furthermore, in some treatment resistant and rapid cycling patients, thyroid gland abnormalities may be observed. The addition of thyroid hormone was reported to increase the effectiveness of lithium with these patients (19).

Before lithium is started, a full blood count should be taken, cardiac rhythm should be assessed with an electrocardiogram, and biochemical tests such as thyroid hormones and liver and kidney functions should be performed. Since the duration to achieve a steady blood level is five half-lives, this is about 5-6 days for lithium. Generally, the starting dose is 300-600mg/day, and although it varies from patient to patient, treatment dose averages at 600-1500mg/day. Age, gender, kidney function, general medical condition, and the patient's response to lithium may be among the factors that determine the dosage and serum level. The serum lithium level during the manic episode is recommended as 0.8-1.2 mEq/L. This upper limit of the therapeutic range might be uncomfortable for some patients. In such cases, the patients are advised to use a lower dose. It is conventionally accepted that lithium is more effective in euphoric mania. It might have dermatological, gastrointestinal, and cardiovascular side effects, as well as side effects related to the thyroid and parathyroid glands and kidneys. When used for prophylaxis, it reduces suicide attempts and mortality rates. However, its narrow therapeutic range, its slowness in taking effect, its potential side effects, and the patients' low compliance to treatment are among the most significant disadvantages that limit the use of lithium (16).

Valproate as monotherapy was significantly superior to placebo (0.55 effect size and 0.25-0.86 confidence interval) and as effective as lithium in randomized studies in the treatment of acute mania (20, 21). Moreover, it was reported to be more effective in cases accompanied by alcohol or drug use and in the presence of neurological disorders, as well as patients with mixed episodes, rapid cycling patterns, and irritable mania (7). Additionally, when used with antipsychotics, valproate enables lower dosage of antipsychotics, quicker response to treatment, and better

outcomes at the end of treatment (22). It is also possible to use valproate in combination with lithium for patients who are unresponsive or resistant to treatment and good responses have been possible with some of them. However, for patients who experience significant side effects, it should be used as briefly as possible and ending the combination treatment is recommended. Valproate is absorbed rapidly from the gastrointestinal tract and reaches its peak levels in the blood in the first four hours. As half-life of valproic acid is short, its prolonged-release form combined with sodium valproate is more widely used. It is glucuronidated in the liver and eliminated by the kidneys. It is known that it may lead to hepatotoxicity and it may increase blood ammonia levels. In the presence of liver problems, ammonia levels may rise significantly and lead to encephalopathy. Furthermore, it is also recommended that pancreatic enzymes are monitored due to the risk of pancreatitis. In women, side effects such as hirsutism and polycystic ovary syndrome, as well as weight gain, tremors, and hair loss may be observed. For bipolar disorder, its therapeutic range is 50–120 mcg/ml. Although it varies among patients, this blood level is achieved with an average dose of 1000–2500 mg/day. Its anti-manic effect can be faster in comparison to lithium. Even though its parenteral form exists, its use in psychiatry has been quite limited. When there is indication for a parenteral medication, antipsychotics with parenteral forms are generally preferred (23).

When used as monotherapy in the treatment of acute mania, carbamazepine was significantly superior in comparison to placebo (24) and it is approved by the FDA in the treatment of acute mania. In studies where carbamazepine was used in combination with lithium (25, 26) and antipsychotics (27), no difference has been observed in terms of effect. Yet, in many guidelines, carbamazepine is not included among the first line treatments. The most important reason for this is not a problem with its effectiveness, but its severe side effects. However, especially for women, situations that require the use of carbamazepine may often arise. Therefore, even though its frequency of use might have decreased, it has not totally disappeared. Moreover, its combined use with antipsychotics has also had successful outcomes (28). Because it is metabolised by the cytochrome enzymes in the liver and due to its hepatotoxic potential, liver functions should be assessed before starting carbamazepine. Additionally, due to its potential for bone marrow suppression, full blood count tests should be done before starting the medication and they should be repeated regularly thereafter. Significant side effects such as teratogenic risk, hyponatremia, and Stevens Johnson syndrome, as well as dermatological ones limit its use during pregnancy. An average dose of 400–1200 mg/day and serum medication level in the range of 4–12 mcg/mL are recommended. Causing less weight gain, feasibility to be used with accompanying neurological disorders, and being more effective in cases with alcohol and drug use are among its advantages. However, its complex drug interactions and severe side effects have caused a significant decrease in its use (24, 25).

ANTIPSYCHOTICS IN THE TREATMENT OF ACUTE MANIC EPISODES

In addition to mood stabilizers, antipsychotics may be used to control some of the symptoms of mood disorders (29). Haloperidol and chlorpromazine are among the first-generation antipsychotics that are shown to be effective in the treatment of acute mania (30). Chlorpromazine is the first agent to acquire indication for acute mania. First-generation antipsychotics are considered potent due their ability to block dopamine receptors at levels as high as 70–80%. Accordingly, they have faster acting effects but they also cause somnolence and extrapyramidal side effects, and thus, their long-term use is limited. Nowadays, they are used in order to get quick results at the initial stages of treatment, especially in cases with agitation and exuberant behaviour requiring rapid control. As second-generation antipsychotics block dopamine receptors at a relatively lower

rate of 50–60%, they are less likely to have extrapyramidal side effects. If side effects such as somnolence and weight gain are managed adequately, first-generation antipsychotics can be used for longer periods. The quality of life of the patient on these medications were claimed to improve significantly in the long term (31). However, metabolic side effects limit the use of second-generation antipsychotics, leading to their use for shorter periods. Being beneficial in cases accompanied by psychotic symptoms, having forms that are appropriate for long-acting parenteral use, and posing less risk of switch to the opposite pole, the use of antipsychotics, particularly second-generation ones, stands out as advantageous in the treatment of acute mania. Since many agents cause similar metabolic side effects, it is recommended that fasting blood glucose and lipid levels; full blood count; urea and electrolytes; liver, kidney, and thyroid hormone tests; blood pressure; pulse; weight; body mass index; abdominal circumference; prolactin levels; electrocardiogram; and if possible drug plasma levels should be monitored.

In controlled studies that they have been prescribed as monotherapy or alongside mood stabilizers, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole and asenapine are among the second-generation antipsychotic agents that have shown to be superior to placebo (7, 15, 32, 33). Olanzapine, risperidone, quetiapine, aripiprazole and asenapine were approved by the FDA for the treatment of acute manic episodes. Olanzapine, aripiprazole, quetiapine and ziprasidone were approved as monotherapy for maintenance treatment as well. Olanzapine, risperidone and quetiapine were approved also to be used alongside mood stabilizers during maintenance treatment. The meta-analysis of randomized controlled studies had shown olanzapine, risperidone and haloperidol to be significantly superior to other mood stabilizers and antipsychotics (32, 34). Such information is vital in the effective and consistent continuation of treatment in the long term. In the treatment of manic episodes, if possible, antipsychotics should initially be started at lower doses and the dosage should be increased gradually depending on the response and side effects. For instance, the starting dose should be as follows: risperidone 2–4 mg/day, paliperidone 6–9 mg/day, olanzapine 5–10 mg/day, quetiapine 300–600 mg/day, and aripiprazole 5–10 mg/day and increased as necessary. One of the new antipsychotics, cariprazine at the dose of 2–4 mg/day has been found not only potent for the manic episode but also effective and reliable for the treatment of the depressive episode (35, 36). In the treatment of manic episodes with mixed features, aripiprazole, asenapine, cariprazine, olanzapine, risperidone and ziprasidone are recommended (37).

For patients resistant to treatment and those who do not want to use medication, acutely effective parenteral antipsychotic drugs are preferred. For example, haloperidol 5–10 mg intramuscular, or rarely intravenous; chlorpromazine 25 mg intramuscular; and zuclopenthixol 50 mg intramuscular are the parenteral first-generation antipsychotics with short-acting effects. They are used in cases when communication with the patient is not possible and/or when treatment is performed against their will, such as states of acute excitation, agitation or delirium. Because of its high risk of neuroleptic malign syndrome and frequency of extrapyramidal side effects, this application should be kept as short as possible and should be replaced by oral treatment as soon as possible.

In cases of low compliance to treatment, or if preferred by the patient, long-acting parenteral forms are implemented as well. Every two weeks flupentixol decanoate 20 mg and zuclopenthixol 200 mg bi-weekly, or haloperidol decanoate 50–100 mg/month are such first-generation antipsychotics. The side effects of first-generation antipsychotics can be seen in long-acting forms as well, so they should be used prudently. Second-generation antipsychotics in long-acting form are olanzapine pamoate 150, 210, 300, 410 mg (150 mg every 4 weeks to 300 mg every two weeks); risperidone microspheres (25, 37.5, 50 mg bi-weekly);

paliperidone palmitate-monthly (50, 75, 100, 150 mg) or paliperidone palmitate-3-monthly (175, 263, 350, 525 mg), and aripiprazole (300-400 mg monthly). The unique clinical phenomenon called “post-injection syndrome” that can be seen with olanzapine pamoate has greatly limited the use of this preparation. Sedation, agitation, confusion, and anxiety can be observed in this syndrome and in order to avoid its consequences, it is recommended that the patient is observed at the clinic for 2-4 hours after the injection. Although long-acting risperidone injection is effective and highly beneficial, its effects are delayed due to the need for 4-6 weeks for the medicine's molecules to dissolve in blood and for the medication to reach a steady efficacy in blood. Paliperidone palmitate and aripiprazole act relatively more rapidly, paliperidone palmitate acts faster than aripiprazole. In the application of long-acting forms of the drugs, the most suitable approach in order to achieve continuity of their effects would be to try their oral treatments for a while to observe their effects and side effects and to switch to the long-acting form after their assessment.

Another second-generation antipsychotic that is not mentioned above is clozapine, which in fact is a significant option in the treatment of resistant cases. Clozapine has been found effective in patients with resistant bipolar disorder (38), those who show mixed features (39) or rapid cycling (40). Because it has proven highly effective also in the other periods of bipolar disorder, it has been claimed that it could be used in the treatment of acute episodes effectively without causing switch to the opposite pole, as well as in maintenance treatment. That is, it is claimed that clozapine could be used as a mood stabilizer (41). However, its severe side effects prevent its prevalent use. Instead, it can be used more easily with valproate and prove highly beneficial. Yet, if used in combination with carbamazepine, its haematological side effect risk increases (42).

OTHER OPTIONS IN THE TREATMENT OF ACUTE MANIC EPISODES

While there are not enough randomized controlled studies on anticonvulsants such as topiramate (43), gabapentin and oxcarbazepine (44), the general outlook for these drugs in the treatment of acute episodes is that they are not significantly effective. Electroconvulsive therapy is an option that can be used during confused/delirious manic episodes (accompanying fever, dehydration and autonomic dysfunction), as well as with patients who are resistant to treatment or in cases with extreme agitation and excitation. In randomized, controlled studies whereby allopurinol is used as supplementary treatment, it is shown to be significantly superior to placebo (45). Tamoxifen was superior to placebo in the treatment of manic episodes both as monotherapy and supplementary to mood stabilizers (46). Likewise, there are studies in which medroxyprogesterone is used supplementary to mood stabilizers, but such use is not recommended (15). In a recent study, it has been shown that the patients' responses to treatment have improved when melatonin is added to lithium and risperidone (47). Moreover, intranasal olanzapine (INP105) and dexmedetomidine film (BXCL501) are considered among the novel agents with potential in treating acute agitation (44). In addition to other treatments, there is also information that the implementation of folic acid may prove beneficial for mania (48). It has been claimed that during manic episodes magnesium decreases agitation, while tryptophan decreases the severity of symptoms. It is also been posited that the addition of choline to treatment during rapid cycling manic episodes had positive impact. However, omega 3 fatty acids have been noted to be not as effective in mania as they are in depression (46).

Electroconvulsive therapy (ECT) is effective during manic episodes; however, because it is an invasive procedure and has negative side effects on memory (49), the indications are limited. Exuberant behaviour that needs to be controlled immediately, catatonic symptoms, resistance to current treatment and causes that limit the use of drugs such as

pregnancy and old age are among the indications of ECT (50, 51). There are studies that found the less invasive repetitive Transcranial Magnetic Stimulation (rTMS) both successful (52, 53) and unsuccessful (54) in the treatment of manic episodes. The supplemental implementation of the rTMS to pharmacological treatments in the conducted studies might have been the cause of contradictory results. Moreover, the methodological differences between the studies might also have resulted in contradictory outcomes. For instance, in the studies the points of application appear to be different. Different regions of application in the rTMS procedure may result in differing effects. Therefore, more controlled studies are needed. In the literature, only one study on transcranial Direct Current Stimulation (tDCS) has been found (55). Still, in studies for other episodes of bipolar disorder, there is promising results for tDCS (56).

CURRENT GUIDELINES FOR THE TREATMENT OF ACUTE MANIA

The algorithm of stepped treatment model serves as a guide for clinicians in the treatment of resistant or difficult patients. While treatment guidelines are being prepared, the available literature is systematically reviewed and available evidence is compiled. Controlled, double blind studies on the efficacy of the drugs are considered primary level of evidence, whereas open label, uncontrolled ones are considered secondary. Case series are assessed as tertiary evidence and for agents which no primary or secondary evidence is present, incident reports and expert assessments are consulted (Table 1). The aim is organising forming stepwise, systematic recommendations for the available treatments

Table 1. Recommended Line of Treatment

Level of Recommendation	Recommendation	Treatment
First-line	Physical examination and workup should be performed; trigger factors should be evaluated; if antidepressants are being taken, they should be stopped; emergency situations should be assessed and if an emergency is present, precautions should be taken.	Monotherapy - quetiapine, risperidone, valproate, lithium; if an emergency is present, olanzapine, haloperidol
Second-line	Compliance to the treatment should be assessed; if there is no response to the first line of treatment despite adequate dose and period of medication, the second line should be implemented.	Monotherapy - olanzapine, haloperidol, carbamazepine; Along with MS - olanzapine, aripiprazole, haloperidol, quetiapine, risperidone, paliperidone
Third-line	Factors that might complicate treatment should be assessed; personal and family history should be examined in detail.	Electroconvulsive therapy in addition to pharmacological treatment; for patients who present mixed features ziprasidone
Fourth-line	Treatments with low levels of evidence can be utilized; drugs recommended at the earlier lines of treatment can be tried.	Chlorpromazine, pimozide, tamoxifen, allopurinol

The recommendations in the table are based on the beneficial and adverse effect profiles of the drugs. MS: Mood Stabilizers

in accordance with the levels of evidence. However, many issues such as prior treatment experience, drug interactions, side effects, and compliance to medications should be considered in the clinicians' choice. Accordingly, agents known to be highly effective may be downgraded in the recommendation algorithm due their side effects. Since treatment guidelines provide recommendations in light of available literature, treatment methods such as ECT and TMS, stand out with their limitations due to difficulties in conducting trials and possibilities of research errors. In medical applications the final decision lies with the clinician (Table-1).

Many guidelines for the treatment of bipolar disorder have been published in the past five years (10, 14, 15, 33, 57). Since they are all prepared according to objective criteria, they have great similarities as expected. There may be differences only in their approaches to side effects and to factors that have an impact on the compliance to treatment, as well as some variations in their order depending on the literature data available at the date of application. Recommendations for the treatment of manic episodes in some guidelines are summarized in Table 2 with their similarities and differences. In the current Canadian treatment algorithm (CANMAT) (14), lithium, quetiapine, valproate, asenapine, aripiprazole, paliperidone, risperidone and cariprazine monotherapies are recommended as the first step of treatment for acute mania, and so are quetiapine, aripiprazole, risperidone and asenapine to be used in combination lithium and valproate. It was reported that approximately half of the patients might respond to the recommendations on the first step of treatment if provided with appropriate dose is and adequate duration of treatment, that is, at least for 3-4 weeks. In the second step of recommendations, in addition to the inclusion of olanzapine, carbamazepine, ziprasidone, haloperidol, lithium or valproate, the combined use of olanzapine with lithium and valproate, as well as ECT are listed. Alternatively, combined use of clozapine, clonazepam, chlorpromazine, carbamazepine and lithium/valproate are recommended; so are rTMS and tamoxifen as monotherapy or in combination with lithium/valproate. However, allopurinol, omega-3 fatty acids and other anticonvulsants are not recommended. Moreover, in cases of agitation, short-acting intramuscular aripiprazole, olanzapine,

lorazepam or inhaled loxapine are recommended as first step. In the second step, once again intramuscular haloperidol, midazolam, ziprasidone or risperidone orodispersible tablet are recommended. Finally, with patients who do not respond to interventions in the first two steps, loxapine, quetiapine or risperidone tablet are recommended in the third step.

In the guidelines prepared by the World Federation of Societies of Biological Psychiatry (WFSBP) (57), evidences in the treatment of manic episodes with mixed features was examined for determining the levels of evidence and recommendation orders. In this list, the order of recommendation is as follows: olanzapine (level of evidence for monotherapy: A; level of evidence for combination: A; second line in recommendations), risperidone (level of evidence for monotherapy: C; level of evidence for combination: E; fourth line in recommendations), aripiprazole and paliperidone (level of evidence for monotherapy: B; level of evidence for combination: E; third line in recommendations), quetiapine (level of evidence for monotherapy: E; level of evidence for combination: C; third line in recommendations), ziprasidone (level of evidence for monotherapy: C; level of evidence for combination: E; third line in recommendations), cariprazine, carbamazepine, valproate (level of evidence for monotherapy: C; level of evidence for combination: F; fourth line in recommendations), gabapentin and first-generation antipsychotics (level of evidence for monotherapy: C, level of evidence for combination: E, fourth line in recommendations), ECT (level of evidence for monotherapy: F, level of evidence for combination: C, fourth line in recommendations) (table-2).

Resistance to treatment is a concern when there has not been more than 50% improvement of symptoms despite the use of standard therapies for eight weeks and therapeutic doses of two different medications - one of these two should be a combination treatment (9, 33). In treatment resistant patients, rapid cycling, mixed features, history of long-lasting depressive episodes and anxiety can be seen (9). Authors have also noted that some of the other factors that could be associated with treatment resistance are gender (more common among women), age (more common among the elderly), later age of onset, familial history of treatment resistance, intense stress factors, accompanying medical comorbidity, personality and temperamental traits, abnormalities in electroencephalography, inflammation, frequent benzodiazepine use, alcohol/drug abuse, lifestyle adversity, lack of insight, and low compliance to treatment. Research on the strategies for treatment of resistant patients is inadequate. In patients whose response to mood stabilizers was inefficient, supplementation with olanzapine, quetiapine, aripiprazole and asenapine resulted in positive outcomes. However, no extra benefit was observed with the supplementation of ziprasidone, topiramate and paliperidone (9). Moreover, the use of mood stabilizers together and in combinations with other medications may provide extra benefit (58). In a randomized-controlled study whereby allopurinol and dipyrindamole were used in combination with lithium, both agents provided additional benefit in the treatment of mania (59). The response rate to ECT among treatment resistant patients is high (50, 51). Response to clozapine, on the other hand, is delayed and present only in high doses (60, 61).

Table 2. Levels of evidence and lines of treatment accepted in the bipolar disorder treatment guidelines published in the past 10 years for the treatment of manic episodes.

	CANMAT		WFSBP*		CINP	RANZCP
	LOE	LOT	LOE1	LOT2	LOE	LOE
Lithium	1	1	F/F	3/5	2	1
Valproate	1	1	C/F	4/3	1	1
Carbamazepine	1	2	C/F	4/-	4	1
Risperidone	1	1	C/E	4/4	1	1
Quetiapine	1	1	E/C	3/2	1	1
Olanzapine	1	2	A/A	2/3	2	1
Aripiprazole	1	1	B/F	3/-	1	1
Paliperidone	1	1	B/E	3/-	-	2
Cariprazine	1	1	C/F	4/-	-	-
Asenapine	1	1	E/F	4/-	1	2
Ziprasidone	1	2	C/F	3/4	-	1
Haloperidol	1	2	C/E	4/-	2	1
Electroconvulsive Therapy	3	2	F/C	4/-	4	-

LOE: Level of Evidence, LOT: Line of Treatment, CANMAT: Canadian Network for Mood and Anxiety Disorders, WFSBP: World Federation of Societies of Biological Psychiatry, CINP: International College of Neuropsychopharmacology, RANZCP: Royal Australian and New Zealand College of Psychiatrists. *Manic episodes with mixed features, A: Clear evidence from controlled studies, B: Unclear evidence from controlled studies, C: Evidence obtained from uncontrolled studies, D: Contradictory information, E: Negative evidence, F: Inadequate information; 1 Monotherapy/combination; 2 Treatment for acute mixed manic episode/Prevention of mixed manic episodes.

CONCLUSION

In this article, pharmacological and other medical therapeutic options in the treatment of acute manic episodes in bipolar disorder are investigated. Whereas olanzapine, haloperidol, and risperidone seem to be suitable options when rapid impact is needed, all antipsychotic drugs are effective in patients with accompanying psychotic symptoms. However, it should be remembered that antipsychotics are not recommended to be used for long term due to their side effects. More studies are needed on the efficacy of novel antipsychotics in the treatment of mania. Yet, mood

stabilizers can also be used in the long term following the treatment of the acute manic episode. Therefore, they remain vital in maintaining consistency in treatment. Aim of the treatment is the cure of the acute episode as soon as possible and enabling the patients to return to their regular life. Medical treatment is enough for the first step; however, for the second step; psychoeducation, psychosocial initiative, and family-oriented therapies should be utilized.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- MIA, TO; Design- MIA, TO; Supervision- MIA, TO, Resource- MIA, TO; Literature Search- MIA, TO; Writing -MIA; Critical Appraisal - TO.

Conflict of Interest: The authors do not report any conflict of interest.

Financial Disclosure: No funding was obtained for this article.

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