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Review Article

New Approaches in the Treatment of Bipolar Disorder

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ABSTRACT

Bipolar disorder is classically delineated as clinically vital episodes of depression and elevated mood with intervening periods of traditional mood. Bipolar depression remains a treatment challenge, with remission rates of solely twenty five to sixty p.c once counseled treatment. Until recently, only quetiapine, olanzapine and fluoxetine were approved to treat bipolar depression. Treatment typically has a pair of phases. Acute-phase treatment is concentrated on the management of the acute mood episodes (manic, hypomanic, or depressive). Maintenance-phase treatment is concentrated on preventing recurrences of acute episodes. In acute treatment settings, patients with bipolar disorders may present with severe agitation, violent behaviors, and psychosis. When this occurs, the goal of treatment is to control dangerous behaviors that may result in harm to the patient or others. Patients can then be safely interviewed and further evaluated. Oral or inhaled pharmacotherapy with benzodiazepines or antipsychotic drugs can be offered to agitated but cooperative patients. However, parenteral antipsychotics, with or without benzodiazepines, may be needed to quickly manage aggressive and violent behaviors. The goal of acute treatment for bipolar depressive episodes is remission. Because remission requires several weeks to occur, a reasonable interim goal is response, defined as a suicidal ideation and psychotic features. Improvement in depressive symptoms must occur without precipitating manic episodes or rapid cycling.

Keywords: Depression, Bipolar disorder, psychosis, violent behaviors, pharmacotherapy, manic episodes

INTRODUCTION

Bipolar disorder is classically delineated as clinically vital episodes of depression and elevated mood with intervening periods of traditional mood. Bipolar depression happens in close to one-hundredth of the globe population and is outlined as a serious depressive episode in patients United Nations agency have toughened a minimum of one episode of mania or hypomania. In most patients with wild depressive unwellness, depressive episodes predominate in frequency and severity; consequently, many patients initially hunt for treatment for depression. [1] Bipolar depression remains a treatment challenge, with remission rates of solely twenty five to sixty p.c once counseled treatment. [5] Until recently, only quetiapine, olanzapine and fluoxetine were approved to treat bipolar depression [2] like different atypical antipsychotics, it antagonizes Dopastat D2 receptors, still as monoamine neurotransmitter 5-HT2A and 5-HT7 receptors. [3,4] monoamine neurotransmitter, noradrenaline, and Dopastat is that the cornerstone of antidepressant drug pharmacotherapy Lurasidone could exert antidepressant drug effects by increasing Dopastat activity within the anterior cortex

through activity at 5-HT2A and 5-HT1A receptors. [7] it should enhance monoamine neurotransmitter activity by down regulation 5-HT2A receptors. [8] Additionally, it should increase noradrenaline by antagonizing alpha1 receptors. [15] Antagonism of 5-HT7 receptors could improve mood. [9]

Management

Treatment Approach

Treatment typically has a pair of phases. Acute-phase treatment is concentrated on the management of the acute mood episodes (manic, hypomanic, or depressive). [10] Maintenance-phase treatment is concentrated on preventing recurrences of acute episodes. [6] Each part is related to specific treatment desires, and obtainable pharmacotherapies have shown differential effectiveness in line with the health problem part. [53] Regular communication between health care suppliers regarding changes in prescribed and over-the-counter medications is important given the chance of clinically vital drug-drug interactions related to medications wont to treat bipolar disorders. [11] Li levels and toxicity risk, as an example, will increase once Li is combined with usually used medications like anti-inflammatory drug medicine and several other medication medications. [29]

CURRENT TREATMENT FOR BIPOLAR DISORDER

The prevalence of morbidity, mortality and prices related to manic depressive illness build its treatment and bar vital goals at intervals medical specialty. [12] There square measure several treatment choices for manic depressive illness. Everybody with manic depressive illness could respond otherwise to treatment, and it's common to need a novel combination of treatments. [13] Usually, treatment entails a mix of a minimum of one mood-stabilizing drug and/or atypical major tranquilliser, and psychotherapy. [14] In general, bipolar disorders may be managed with applicable pharmacotherapy and targeted psychosocial interventions, however residual clinical symptoms and pathology will persist, even with active treatment. [52] Therefore, mood symptoms and functioning should be frequently reevaluated once treating patients with bipolar disorders. The foremost wide used medication for the treatment of emotional disorder embodies major tranquilliser and anticonvulsant drug. [17] Major tranquillisers are often remarkably effective in reducing mania. [18] Lithium may forestall repetition of depression, however its worth looks bigger against mania than depression; so, it's typically given in conjunction with alternative medicines proverbial to possess bigger worth for depression symptoms. [19] Valproic acid may be a mood stabilizer that's useful in treating the frenzied or mixed phases of emotional disturbance, [20] in conjunction with carbamazepine another medicine. These medicines could also be used alone or together with metal to manage symptoms. [21] Lamotrigine another antiepileptic drug has been shown to have value for preventing depression and, to a lesser degree, manias or hypomanias. [22] New antipsychotic medications, such as aripiprazole, asenapine, olanzapine or risperidone are often given to patients as an alternative to lithium or divalproex. [23] They also may be given to treat acute symptoms of mania particularly psychosis before lithium or divalproex can take full effect, which may be from one to several weeks. [24] Another antipsychotic, lurasidone, is approved for use in bipolar I depression as is the combination of olanzapine plus fluoxetine. The antipsychotic quetiapine is approved to treat bipolar I or II depression. Preliminary studies also suggest that the atypical antipsychotic cariprazine also may have value for treating bipolar depression. [25]

1. Acute Behavioral Emergencies

In acute treatment settings, patients with bipolar disorders may present with severe agitation, violent behaviors, and psychosis. When this occurs, the goal of treatment is to control dangerous behaviors that may result in harm to the patient or

others. [46] Patients can then be safely interviewed and further evaluated. Oral or inhaled pharmacotherapy with benzodiazepines or antipsychotic drugs can be offered to agitated but cooperative patients. [54] However, parenteral antipsychotics, with or without benzodiazepines, may be needed to quickly manage aggressive and violent behaviors. [55]

2. Acute Manic or Hypomanic Episodes

a. Manic Episodes

Mania is considered a medical emergency, often requiring psychiatric hospitalization. [15] Goals of treatment include rapid stabilization of manic symptoms and dangerous behaviors, restoration of sleep, and, often, concurrent management of withdrawal from drugs and alcohol. [51]

Pharmacotherapy Options for Acute Manic or Hypomanic Episodes

Medication name	Starting dose	Effective dose (drug level)	Treatment priority and comments
Monotherapy, mood stabilizers			
Lithium	300 mg bid-tid	Usually 900-1800 mg (0.8-1.2 mEq/L)	First line; often combined with other mood stabilizers or antipsychotics for severe or psychotic mania
Divalproex	250 mg bid-tid	Usually 1250-2500 mg Loading dose 20-30 mg/kg body weight (50-125 µg/mL)	First line; often combined with other mood stabilizers or antipsychotics for severe or psychotic mania High priority for rapid cycling patients Usually avoided in women of reproductive age
Carbamazepine	100-200 mg bid	800-1600 mg (4-12 µg/mL)	Second line
Monotherapy, antipsychotic drugs—generally higher priority than mood stabilizer monotherapy for patients with psychotic symptoms, especially those with established maintenance-phase efficacy			
Aripiprazole	10-15 mg/d	15-30 mg/d	First line; may be higher priority for rapid cycling patients
Asenapine	5-10 mg bid	10 mg bid	First line
Cariprazine	1.5 mg/d on day 1 3 mg/d on day 2	3-12 mg/d	First line
Paliperidone extended release	3-6 mg/d	6-12 mg/d	First line
Quetiapine	50 mg bid (300 mg/d when using the extended release form)	400-800 mg/d	First line; may be higher priority for rapid cycling patients
Risperidone	0.5-1.5 mg bid	1-6 mg/d	First line[‡]
Ziprasidone	40 mg bid	60-80 mg bid	First line; all doses must be taken with food
Olanzapine	10-15 mg/d	10-30 mg/d	Second line
Typical antipsychotics	Haloperidol (0.5-2 mg bid-tid) Chlorpromazine (10-50 mg bid-tid)	Haloperidol (6-20 mg/d) Chlorpromazine (300-800 mg/d)	Third line; usually combined with mood stabilizers for severe or psychotic mania; typically not used beyond the acute phase of treatment.

For most patients, the acute antimanic effects of pharmacotherapy unfold over several days, and almost always within 3 weeks. [56] Manic episodes that do not respond to conventional pharmacotherapy (including drug combinations) may benefit from clozapine (usually combined with mood stabilizers) or electroconvulsive therapy. [57] Some patients with refractory mania may respond to experimental tamoxifen or allopurinol when added to lithium-based pharmacotherapy. [58]

b. Hypomanic Episodes

Hypomanic episodes are not associated with either psychosis or significant dysfunction and are managed in ambulatory settings. Pharmacotherapeutic options for hypomania are similar to those for mania. [51] Monotherapy with mood stabilizers with or without adjunctive benzodiazepines can be used for the initial treatment of hypomanic episodes. [54] Pharmacotherapy with an antipsychotic drug, or combination therapy with 2 mood stabilizers or mood stabilizers combined with antipsychotic drugs. [60]

3. Acute Bipolar Depressive Episodes

Acute bipolar depressive episodes are generally managed in ambulatory settings. Psychiatric hospitalization is

usually needed for bipolar depressed patients at imminent risk for suicide, those with severe agitation or psychotic features, or those with severe loss of functioning to the point that they can no longer adequately care for themselves clinically significant reduction in the number and severity of mood symptoms, with resolution. [16] The goal of acute treatment for bipolar depressive episodes is remission. [1] Because remission requires several weeks to occur, a reasonable interim goal is response, defined as a cli suicidal ideation and psychotic features. Improvement in depressive symptoms must occur without precipitating manic episodes or rapid cycling. 6For those with comorbid substance use disorders, dual treatment of bipolar depression and the substance use disorder(s) is recommended. Psychosocial treatment as an adjunct to pharmacotherapy for bipolar depression. [59]

a. BP-I Depression

Depressive episodes account for greater disability and adverse functional impact than manic or hypomanic episodes. [61] Relatively few medications have been shown to be effective for treating acute bipolar depressive episodes. [62] Treatment options for new bipolar depressive episodes with no active pharmacotherapy. [63] Monotherapy with quetiapine or lurasidone and combination pharmacotherapy with lithium and lamotrigine, and either quetiapine or lurasidone plus a mood stabilizer (lithium or valproate), are high-priority treatment options for acute BP-I depression. [64]

4. Evidence-based treatment recommendations

The mainstay of therapy for all three phases of bipolar disorder (mania, depression, and prophylaxis) is pharmacological. [27] The first-line treatment for mania is an antipsychotic. [26] Bipolar depression is often long lasting and difficult to treat, requiring a different approach from that used in unipolar depression [28] showed that the combination of lamotrigine and quetiapine is more effective than quetiapine alone in patients with bipolar depression. There is some evidence that the atypical antipsychotic lurasidone may have particular efficacy in bipolar depression with mixed features, [29] and preliminary data support use of armodafinil as an adjunctive therapy. [30,31] Intravenous ketamine as an add-on therapy to mood stabilizers shows potential to have a rapid but often transient antidepressant effect. [32] Finally, a recent study highlights that electroconvulsive therapy remains a useful option for treatment-resistant bipolar depression. [33] For prevention of relapse in bipolar disorder, lithium remains the most effective [34] Studies support efficacy of a number of interventions, but only quetiapine and lithium prevented recurrence of both polarities of mood episode. Olanzapine, risperidone, and lithium in combination with valproate were significantly better than placebo in the prevention of manic episodes, and lamotrigine was better than placebo for depressive relapse. Valproate did not differ from placebo when depression and mania were considered separately. [35] It is also noteworthy that, from a methodological viewpoint, the quality of the studies included in the meta-analysis varied considerably, and these differences affected the final ranking of treatments. [14] The efficacy of lithium was observed even when trial designs favored the active comparator. Hence, despite not being particularly well tolerated, lithium was supported as first-line treatment; quetiapine, olanzapine, and lamotrigine were considered second line. [37] In a recent systematic review, [36] the authors concluded that the evidence is strongest for psycho education in the prevention of relapse in the early years after onset of bipolar disorder, with much more limited evidence for the use of cognitive behavioral and interpersonal therapies in the acute phases of the illness. [49]

5. Non pharmacological treatment

Trauma and stress can directly cause or influence symptoms and these may be unknown to family members and supporters.

People with bipolar who receive intensive psychotherapy were 58% more likely be well in a given month and had higher rates of recovery than individuals only receiving collaborative care. [48]

- **Cognitive Behavioral Therapy (CBT)**

CBT is based on the idea that thoughts drive our emotions and actions, and behaviors and emotions influence how we think. [38] By exploring unhelpful Thought- Emotion Action cycles people can learn how to modify them. [46] As a result, they become happier and more able to weather adversity and create meaningful lives for themselves. CBT teaches people not so much how to control their world, but how to control the way they interpret and respond to their world. [39] It is predicated on the belief that events don't cause our emotions; emotions are caused by the way we interpret and give meaning to events. [47] CBT can help break vicious cycles of negative thinking, feelings, and behaviors that influence mental health symptoms. CBT has proven to work on many levels for bipolar, decreasing relapse rates, depression, and mania while improving psychosocial functioning. [40] CBT is generally short-term and structured, with homework between sessions. It uses a problem-solving and goal-directed approach to address mental health issues. It can be taken in many forms including face-to-face, apps, on-line tools, and group sessions. Online therapist-to-client matching services can help. [41] Versions of CBT that are not face-to-face are considerably less expensive and easier to schedule than therapist-led CBT and are as effective as face-to-face CBT therapy if therapist support is provided. [42]

- **Interpersonal and Social Rhythm Therapy (IPSRT)**

IPSRT is founded upon the belief that disruptions of our circadian rhythms (our body's "clock") and sleep deprivation may influence symptoms of bipolar. [43] IPSRT establishes daily rhythms for routines and sleep cycles, using active and social stimulation designed to moderate moods and relieve symptoms. [44] When IPSRT is used during acute bipolar episodes, individuals have significantly longer periods of stability, far greater regularity in daily routines, and 24 improved functioning at work.[45] Intensive psychological interventions and family involvement are 25 important ingredients for the best outcomes in bipolar. [50]

CONCLUSIONS

Currently, psychiatrists dispose of a therapeutic arsenal of 13 different drugs approved by regulatory agencies to address the different acute episodes of bipolar disorder and the prevention of relapse. The treatment is only effective if the treatment is combined with psychotherapy.

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