Mixed States in Bipolar Disorder: Etiology, Pathogenesis and Treatment

Ather Muneer*

Islamic International Medical College, Riphah International University, Rawalpindi, Pakistan

Many bipolar disorder patients exhibit mixed affective states, which portend a generally more severe illness course and treatment resistance. In the previous renditions of Diagnostic and Statistical Manual mixed states were narrowly defined in the context of bipolar I disorder, but with the advent of DSM-5 the term "mixed episode" was dropped and replaced by "mixed features" specifier which could be broadly applied to manic, hypomanic and depressive episodes in both the bipolar spectrum and major depressive disorders. This paradigm shift reflected their significance in the prognosis and overall management of mood disorders, so that the clinicians should thoroughly familiarize themselves with the contemporary notions surrounding these conditions. The purpose of this manuscript is to bring to light the current conceptualizations regarding the etiology, pathogenesis and treatment of mixed states. To achieve this goal, in June 2016 an extensive literature search was undertaken using the PubMed database. Some exploratory terms utilized included "mixed states", "mixed episodes", "switching", "rapid cycling" cross referenced with "bipolar disorder". Focusing on the most relevant and up to date studies, it was revealed that mixed states result from genetic susceptibility in the circadian and dopamine neurotransmission apparatuses and disturbance in the intricate catecholamine-acetylcholine neurotransmission balance which leads to mood fluctuations. The management of mixed states is challenging with atypical antipsychotics, newer anticonvulsants and electroconvulsive therapy emerging as the foremost treatment options. In conclusion, while progress has been made in the neurobiological understanding of mixed states, the currently available therapeutic modalities have only shown limited effectiveness.

Key Words: *Bipolar Disorder; Depressive Disorder, Major; Acetylcholine; Catecholamines; Dopamine*

Corresponding Author:
Ather Muneer
*Islamic International Medical College,
Riphah International University, 274
Peshawar Road, Rawalpindi 4422,
Pakistan*
Tel: +92−51−548−1828
Fax: +92−51−512−5170
E−mail: muneerather2@gmail.com

INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric ailment with typical onset in adolescence or early adulthood. While the index episode may manifest as melancholic depression, hypomanic or manic exacerbations may occur later on in the course of the disease and are the sine qua non of the diathesis. It is a prevalent condition and innumerable people are afflicted globally, irrespective of sex, race and geographic location. Vast numbers of patients follow a pernicious course, with adverse sequelae in the biopsychosocial realm. Negatively influencing the prognosis are such factors as repeated mood episodes, mixed affective symptoms, psychiatric and medical comorbidities. The etiopathology of the illness is still unknown and treatments are mainly palliative rather than curative in nature. A particularly difficult matter in the management of bipolar patients is the occurrence of mixed states and the purpose of the present manuscript is to comprehensively address this issue. The strategy adopted in searching the existing literature is first described, followed by a detailed account of the clinical significance of mixed symptoms. Then, the current conceptualizations regarding the etiology and pathogenesis of mixed states are explained, and finally evidence-based

treatment options are discussed.

SEARCH STRATEGY

In June 2016 the PubMed electronic database was explored using a variety terms, for example "mixed states", "mixed episode", "switching", "rapid cycling" cross-referenced with "bipolar disorder". A very large number of citations exceeding 1,000 were retrieved with this strategy which included clinical trials, retrospective and prospective studies, animal experiments, review articles and case reports. These covered various aspects like causation, clinical characteristics and management. In order to gain a current perspective, papers published in the last 10 years were selected which still numbered over 500; further, it was noticed that the number of publications has increased several fold in the last decade or so. The abstracts of these articles were read and their pertinence to the topic under discussion was determined. About 100 articles were found to be particularly relevant and were comprised of human and animal studies and review articles, which shed light on the subject from different angles. These were read in full and their reference lists were also consulted. The emerging themes from this endeavor were synthesized in a succinct and applicable style to delineate the modern stance on the etiology, pathogenesis and treatment of mixed affective states in bipolar disorder.

MIXED SYMPTOMS IN BIPOLAR DISORDER

1. Historical developments regarding the concept of mixed phenomena

In BD, patients suffer from severe mood fluctuations which range from major depressive episodes (MDE) to manic or hypomanic exacerbations. Recognized by Kraepelin and described in the 8th edition of his textbook, mixed s ○ tates have a high prevalence rate in this ailment.[1] Since that era, the definition and conceptualization of mixed states

has varied, but with the introduction of the Diagnostic and Statistical Manual's 5th edition (DSM-5) in 2013, this notion has crystallized and broadened.[2] In the preceding DSM-IV-TR, mixed episode was defined in the context of BD type I as an occurrence typified by the concurrent presence of full manic and depressive phenomena in an individual for at least seven days. This narrow definition was radically modified in DSM-5, with its redefinition that the presence of only three symptoms of opposite mood polarity was sufficient to qualify for the specifier "with mixed features". Moreover, this specifier could be used for a manic episode in BD type I, hypomanic episode in BD type I or II, as well as for an MDE in major depressive disorder (MDD).[3] The paradigm shift reflected the accumulated research evidence which emphasized the importance of mixed symptoms in the clinical, functional, and therapeutic spheres of affective disorders.[4] Fig. 1 gives an illustrative account of the current understanding of mixed states throughout the entire spectrum of mood disorders and is reflective of the widening of this concept. Table 1 provides an overview and diagnostic features of incumbent affective states according to DSM-5.

2. Broadening of the concept of mixed states

Within the framework of DSM-5 the extension of the perception of mixed states implies that in an affective episode, clinicians are able to diagnose patients with only few concomitant symptoms of opposite mood polarity. Essentially, this shows that bipolar and MDD patients are more likely to be considered as having mixed episodes, and while this is the modern rendition of a century old idea espoused by Kraepelin, it has significant ramifications for the pathogenesis and treatment of these ailments. Approximately 40% of patients have mixed episodes, but this figure may be much higher within the context of DSM-5.[5] For the improved management of these conditions, it is therefore necessary to cultivate a better understanding of the neurobiology and longitudinal course of mixed states.

Manic/hypomanic episode	Depressive episode	Episode with mixed features

· Elevated/expansive mood
 · Inflated self-esteem/ grandiosity
 · Overtalkativeness/ pressure of speech
 · Flight of ideas/racing thoughts
 · Increased energy/goal directed activities
 · Increased risky activities
 · Decreased need for sleep
	· Prominent depressed mood
	 · Anhedonia
	 · Significant weight loss or gain
	 · Insomnia or hypersomnia
	 · Psychomotor agitation or retardation
	 · Loss of energy
	 · Feelings of worthlessness or guilt
	 · Decreased concentration/ indecisiveness
	 · Suicidal ideation/attempt
		· Three or more manic/ hypomanic symptoms in an MDE
		   - BD type I
		   - BD type II
		   - MDD
		 · Three or more depressive symptoms in a manic or hypomanic episode
		   - BD type I
		   - BD type II

FIG. 1. Diagnostic criteria for manic, depressive and mixed states according to DSM-5. As opposed to previous editions, in DSM-5 the specifier "with mixed features" is used for manic, hypomanic or depressive episodes in bipolar spectrum and major depressive disorders. The term "mixed episode" used in the context of bipolar disorder type I has been discontinued in DSM-5. BD: bipolar disorder, MDD: major depressive disorder, MDE: major depressive episode.

TABLE 1. Diagnostic features of different affective states according to DSM-5

Symptom domain	Hypo/manic episode	Depressive episode	Episode with mixed features
Subjective mood	Elated.	Depressed.	Varies.
Hedonic tone	↑ involvement in pleasurable activities.	Anhedonia.	Mixture of both.
Thought content	Grandiose.	Worthlessness/guilt.	Varies.
Talk	↑ in rate, rhythm and volume.	↓ in rate, rhythm and volume.	Incongruent e.g. depressed mood with pressure of speech.
Behavior	Risky behaviors.	Suicidal acts.	Contrasting e.g. elevated mood with suicidal ideation.
Energy	↑	↓	↑ ↓
Sleep	↓ need for sleep.	Early morning wakening.	Severely disturbed.
Thoughts	Racing thoughts.	Difficulty in thinking/ concentration.	Incongruent e.g. depressed mood with racing thoughts.
Appetite/weight	Disrupted meal schedule.	↓	Severe disruption.
Duration	Hypomania-4 days; mania-7 days.	14 days.	Duration criteria no longer apply.
Minimum criteria	3 depressive features in hypomanic or manic episode.	3 manic features in a depressive episode.	Mixed hypomania-BD type I or II. Mixed mania-BD type I. MDE with mixed features-BD type I or II/MDD.
Functioning	Hypomania-impaired but does not require hospitalization. Mania-severely impaired/may need hospitalization.	Impaired according to degree-mild/ moderate/severe.	Varies according to diagnosis.

BD: bipolar disorder, MDD: major depressive disorder, MDE: major depressive episode.

3. Clinical impact of mixed symptoms

In the perspective of bipolar disorder, recurrent euphoric mania occurs in a small subset of cases comprising about 30% of the patients, whereas dysphoric or mixed mania is much more prevalent.[6] Bipolar patients tend to have repeated episodes of the same type, so that those suffering from mixed episodes are prone to exhibiting the same type of symptoms time and again. They suffer from greater comorbid conditions, chief among which are anxiety spectrum disorders and ailments due to substance misuse. Furthermore, due to the presence of depressive phenomena in activated states, these patients are also at greater risk of completed suicide.[7] Another factor negatively influencing the prognosis is susceptibility to rapid cycling, in which patients have brief if any euthymic periods and a persistent symptomatic state is evident throughout the course of the illness. These facts allude to the pernicious nature of mixed symptoms, so that the treating physician must be alert to their presence and be prepared to institute therapeutic strategies which are effective, well tolerated, and have a good safety profile.[8] Fig. 2 provides a pictorial outline of the burden imposed by mixed affective symptoms on the illness course in bipolar disorder, with a depiction of the long term adverse consequences.

FIG. 2. The burden of mixed symptoms in bipolar disorder. In bipolar disorder mixed states portend a pernicious course with increased suicidality and poor psychosocial functioning.

4. Clinical trajectory of bipolar disorder

While the onset of BD is frequently in adolescence or the early teenage years, the first manifestations are varied and often confusing. A youn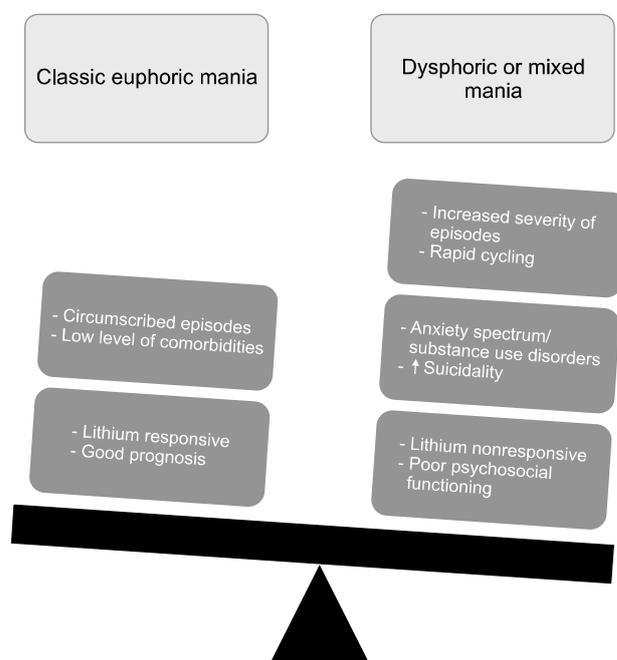g adult can present with an initial episode of melancholic depression, or alternatively with a disturbance of conduct like oppositional defiant disorder or attention deficit hyperactivity disorder. There may be psy-

chosocial perturbation with emotional dysregulation, substance misuse and involvement in risky behaviors. In this regard, family history may be suggestive, with the presence of bipolar disorder in 1st degree relatives, but many symptomatic youth have close family members suffering from such diverse neuropsychiatric conditions as anxiety spectrum disorders, substance dependence, or psychotic spectrum disorders.[9] With the present state of knowledge there are still no validated biomarkers for BD, so that the treating physician has to take a longitudinal perspective and manage such cases empirically. The course of BD is malignant in a substantial minority of cases, and as pharmacotherapuetic options are limited and there is a presence of treatment refractoriness, it is a serious issue.[10] Repeated affective episodes of increasing severity have a pervasive, negative effect on all aspects of functioning, with adverse sequelae in the biopsychosocial realm. In this scenario, it is essential to inculcate better knowledge of the neurobiological underpinnings of affective exacerbations, particularly the pathogenesis of manic and depressive episodes, the homeostatic disturbances characterizing mixed states, and neurochemical alterations driving the switch process.

ETIOLOGY AND PATHOGENESIS OF MIXED STATES IN BIPOLAR DISORDER

1. Circadian dysregulation hypothesis of mood disorders

Mood disorders are exemplified by disruption in the sleep-wake schedule, disturbance in daily activity levels, and irregularity of meal times, signifying a profound disorder in the circadian system.[11] While these aspects of affective illnesses have recognized since the mid-20th century, research in the past few decades has progressively clarified the etiopathological mechanisms underpinning this correlation.[12] It has now become obvious that circadian rhythm disturbance is at the core of mood disorders and this section of the review will outline the findings from the extant literature in this regard, with particular reference towards the induction and perpetuation of mixed states.

It has been demonstrated that in patients with BD, mood exacerbations are provoked by alterations in the intensity of light and also follow seasonal patterns.[13] Further, bipolar subjects show irregularities in key biological processes that are under circadian control, for example sleep, diurnal activity, hormone levels and body temperature.[14] Mood stabilizing medications such as lithium act to reinstate some of these disrupted rhythms by producing a robust phase-delay in daily oscillations and increasing rhythmic amplitude, which may be the key to their therapeutic effects.[15] With the identification and replication of the individual genes that constitute the molecular clock, it is now possible to investigate the molecular mechanisms that underlie the association between the circadian system and mood disorders. Additionally, new insights are developed that inform us about the pathogenesis of different phenotypes within affective disorders, such as mixed states and their relationship to the dysregulation of the circadian machinery.[16] A brief description of the molecular clock follows to clarify the sub-cellular events that epitomize the daily, rhythmic oscillations across the mammalian species.

2. The molecular clock

The main molecular clock is housed in the suprachiasmatic nucleus (SCN) in the hypothalamus, and is formed of a transcription-translation circuit which oscillates over the duration of about 24 hours, without the contribution of external environmental cues. The chief activator of transcription is comprised of a dimerized complex of Circadian Locomotor Output Cycles Kaput (CLOCK) protein and Brain and Muscle ARNT-like Protein 1 (BMAL1). This molecular composite binds to Enhancer-box sequences in the promoters of many genes including the *Period* (*Per*) and *Cryptochrome* (*Cry*) genes. The PER and CRY proteins are translated in the cytoplasm and are phosphorylated by the priming enzyme, casein kinase 1ϵ before being targeted by glycogen synthase kinase 3β, causing alterations in their viability, relationship, and capacity to enter the nucleus. Upon DNA binding, these inhibit the actions of the CLOCK/BMAL1, thus forming a negative feedback loop. Furthermore, there is another closely related loop in which the CLOCK/BMAL1 activate the transcription of orphan nuclear receptor genes *Rev-erb*α and *Ror*α which act to repress and activate the transcription of *Bmal1* and *Clock*, respectively through their interaction with the ROR elements. As alluded to above, many controlling kinases, phosphatases, and secondary feedback loops act on the molecular clock, contributing to further intricacy in the circadian apparatus.[17] Significantly, circadian transcription factors are involved in the regulation and functioning of several other clock-controlled genes, which partake in a whole range of homeostatic actions in every body system. In essence, it is now believed that approximately 50% of the mammalian genes are expressed rhythmically, which participate in a wide array of biological and behavioral functions.[18]

3. Switch process in bipolar disorder

In BD, every patient shows signs of manic and depressive symptoms to a greater or lesser extent and varying pathophysiological mechanisms expectedly trigger these affective changes. There is a whole gamut of presentations, as some patients have rapid fluctuations in symptomatology extending over days and weeks, while other more severe cases have concomitant manic and depressive manifestations that alternate over a matter of hours, a phenotype sometimes referred to as ultra-rapid cycling bipolar disorder.[19] For effective treatments, the mechanisms underlying switching between states need to be discovered, and this aspect is aptly regarded as the "holy grail of BD research". In this respect, important insights have been inculcated by studying the switch process brought about by pharmacotherapuetic and chronobiological measures employed for the management of mood disorders.[20]

4. Pharmacological triggers of switching

Patients with bipolar depression treated with different classes of antidepressants exhibit varying frequency of change over into manic or hypomanic states, and mixed episodes are also reported to occur with higher frequency in such cases. Long term treatment with tricyclic antidepressants (TCAs) has time and again been associated with producing this affective change over in up to 70% of recipients.[21] TCAs mainly act to block the re-uptake of serotonin and norepinephrine from the synaptic cleft and these combined blockers produce manic/hypomanic switches with greater regularity than selective serotonin re-uptake inhibitors.[22] Bupropion, a dual norepinephrine/dopamine re-uptake blocker also causes switches in about 20% of treated cases, and this occurs in spite of co-treatment with mood stabilizers. It therefore appears that increasing synaptic levels of norepinephrine or dopamine via re-uptake inhibition likely provokes change over from depression to hypomania or mania, as well as results in the induction of mixed states even when mood stabilizers are employed adjunctively.[23]

Alternatively, directly enhancing norepinephrine/dopamine levels also results in mania-like behavior. For instance, therapeutic administration of L-dopa to Parkinson's disease patients can provoke mania like behaviors such as gambling and increased risky activities.[24] Furthermore, indirect dopamine/norepinephrine augmentation by amphetamine, a combined re-uptake inhibitor, can cause manic/hypomanic exacerbations in euthymic bipolar patients, and instigate behavior resembling mania in well individuals. Confirmation of these effects is derived from research which shows that alterations of dopamine/norepinephrine re-uptake sites can modify the behavioral outcomes of amphetamines.[25]

Tyrosine hydroxylase (TH) is the rate limiting enzyme in dopamine biosynthesis so that administration of the TH inhibitor α-methyl-para-tyrosine (AMPT) causes depletion of catecholamines, and reduces symptoms of mania while increasing depressive manifestations. In one study, hypomania was induced in euthymic bipolar patients after revival from a catecholamine reduction caused by AMPT, making it apparent that the regulation of catecholamines with over-activity is important for switching to an activated state, whereas the opposite may be true for depression.[26,27]

There is much less information about pharmaceutical agents that can cause switching to a depressive episode. Physostigmine, a medication employed to enhance memory in Alzheimer's disease is an acetylcholinestrase inhibitor which prevents the breakdown of acetylcholine, thus ultimately increasing its synaptic levels. It can decrease manic symptoms in BD cases, moreover in healthy individuals and remitted cases this medication can produce a state of depression. To extend these findings further, recent work has shown that enhanced acetylcholine levels are seen in subjects with both unipolar and bipolar depression.[28] Additionally, there is change in the expression of cholinergic receptors in bipolar subjects, giving credence to the notion that elevated acetylcholine levels purportedly induce a depressed state in BD patients.[29]

The working of other neurotransmitters has been studied to investigate the phenomenon of switching in BD. Both lamotrigine and riluzole are inhibitors of glutamate release and neither of these has been associated with the switch process. Particularly, the former medication is frequently used in the depressed and maintenance phases of BD, but studies have repeatedly shown that lamotrigine is not associated with switching into manic/hypomanic states, does not induce mixed episodes, nor does it lead to rapid cycling.[30] Intravenous administration of ketamine, an NMDA receptor antagonist is an emerging treatment for depression, including bipolar depression. No incidence of ketamine induced switching in depressed bipolar patients has been reported, making it unlikely that glutamatergic signaling is involved in the switch process.[31]

Fig. 3 provides an illustrated adaptation of the neurochemical imbalance hypothesis of bipolar disorder and emphasizes the continuum in symptomatology during the course of the illness.

5. Chronobiological considerations

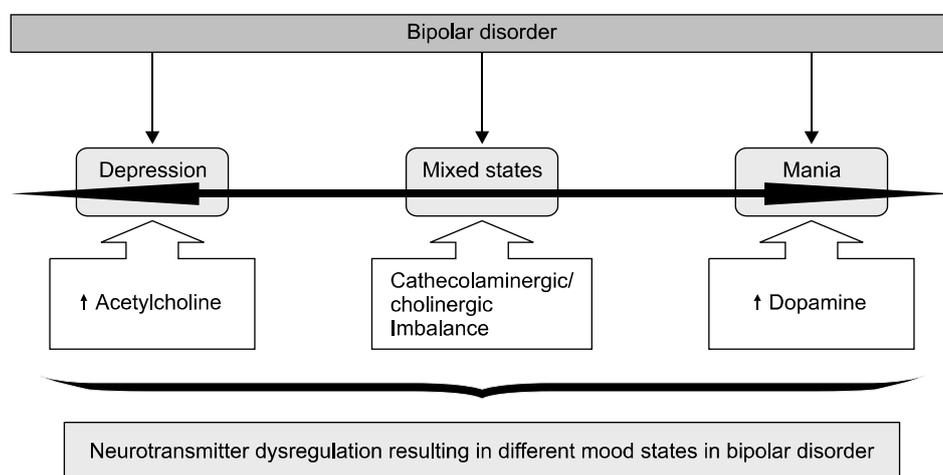In euthymic, unmedicated patients, the switch into ma-

FIG. 3. Neurotransmitter basis of affective states in bipolar disorder. Data from different lines of evidence, but most importantly from the administration of pharmacological agents has elucidated the neurotransmitter abnormalities underlying different mood states in bipolar disorder. This hypothesis posits cathecholaminergic/cholinergic imbalance as central to the pathogenesis of mixed states. See text for further details.

nia has been documented with irregular sleep patterns, along with increase in catecholamine release.[32] Complete lack of sleep can result in manic exacerbation in up to 30% of bipolar patients, and can also cause mania like behavior in healthy controls.[33] These observations support the social rhythm disruption or social zeitgeber theory of mood disorders, which speculates that a disturbance in social/biological rhythms can induce affective episodes in susceptible people. Such disruptions can include stressful life events, irregular daily schedules and chaotic life style with disarray in sleep and meal times, while circadian disturbances caused by shift work, transmeridian travel, etc can also precipitate mood episodes.[34] Hence, circadian rhythm irregularities are a major contributor in the pathogenesis of BD, whereas all effective treatments essentially resynchronize the biological clock.

In this vein, it must be understood that changes in seasons are among the most important environmental triggers for precipitation of mood episodes.[35] In seasonal affective disorder (SAD), vulnerable individuals experience depressive exacerbations during autumn and winter months, corresponding to shortening of the day. Early morning bright light therapy has a phase advancing effect and is therapeutic in SAD, however it is also known to cause switching into mania, as well as inducing mixed states.[36] Further, bipolar patients experience manic episodes at a higher rate during spring and summer months with the lengthening of the period of the day.[37] Significantly however, seasonal variations in BD are correlated to a positive family history, and thus the illness has a heritable component making this a genetic-based condition with an affirmative history of the disorder in family members in 60-80% of cases.

6. Clock genes in bipolar disorder

Several genome wide association studies (GWAS) have been undertaken in BD but statistically significant correlations have not been forthcoming. This may be because BD is a diverse condition and the patient populations studied were too heterogeneous to provide meaningful results. As such, studying sub-sets of patients with phenotypic similarity can be more informative. In a GWAS on subjects self-proclaiming as having seasonal recurrences of mania versus non-seasonal bipolar cases, an SNP rs41350144 lying within the intron of neurofibromin 1A gene on 1p31 was found to have a statistically significant association in the former sub-population.[38] More significantly however, genes involved in the circadian mechanism have also been implicated in BD. In one study, a causal relationship concerning SNPs in 10 CLOCK related genes which included *ARNTL, CLOCK, CRY2, CK1Є, DBP, GSK3β, NPAS2, PER1, PER2* and *PER3* were investigated. Haplotype analyses in *ARTNL* and *PER3* genes were found to be meaningfully connected to BD in the 159 families included in the study.[39] There are several other studies that have identified polymorphisms in the circadian apparatus using candidate gene approaches, whose detailed description is beyond the scope of this review. However, it can be argued

that circadian rhythm abnormalities are the cause rather than the effect of mood disturbances.[40]

Importantly, rodent models with genetically engineered mutants have shed light on the involvement of circadian genes in mood disorders. Mice created by inducing an alteration in the *Clock* gene (*Clock△19*) have a phenotype comparable to mania in BD. Intriguingly, when these animals are administered the prototype mood stabilizer, lithium, their behaviors in large part normalize resembling those of wild type mice.[41] Mutations in other CLOCK genes result in similar behavioral phenotypes, a prime example being of transgenic mice overexpressing GSK3β exhibiting manic like profiles.[42] Utilizing *Clock△19* mice, revealing experiments have shown the link between circadian genes, neurotransmitter functional control, and behavioral phenotypes of high clinical relevance.

In an attention-grabbing study mutant mice were engineered by RNA interference using short hairpin RNA (shRNA) and viral utilized gene transmission to silence *Clock* expression exclusively in the ventral tegmental area (VTA). The animals were next subjected to a range of behavioral, molecular, and physiological measures. It was discovered that disabling *Clock* specifically in the VTA resulted in hyperactivity and reduction in anxiety-related behaviors akin to the profile of the *Clock△19* animals. Interestingly, VTA exclusive *Clock* silencing also caused a significant rise in depression-like behavior, generating a largely manic-mixed picture. Furthermore, VTA knock-down of *Clock* also changed circadian period and amplitude, implicating *Clock* in the VTA in the control of daily oscillations. VTA dopaminergic neurons carrying the *Clock* shRNA fired at a greater rate than the non-transfected neurons. *Clock* disabling altered the expression of several ion conduits and dopamine-associated genes in the VTA which could be responsible for the manifest phenotype in the modified strains. As a whole, these observations implied a major function for CLOCK in the VTA in the control of dopamine neurotransmission, expression of behavioral profile reminiscent of mixed states, and dysregulation of circadian rhythms.[43]

The above mentioned findings were further extended in a more recently published study which again utilized the *Clock△19* mice having a polymorphism in the CLOCK gene. The latter is a core regulatory constituent of the circadian transcription machinery and *Clock* mutant mice display increased activity, more reward seeking and reduced anxiety and depression like behaviors, resembling mania in humans. Mice are nocturnal animals and genetically modified strains express this phenotype during daytime; their period of inactivity. Concomitant with this profile, there is increased firing of VTA dopaminergic neurons, which is in line with altered mesolimbic dopaminergic activity observed in human mania. In an elegantly designed study, the interconnection between circadian gene interference and rapid mood cycling/switching was demonstrated. *Clock△19* mice were used as these exhibited rapid changes in behavior with an intense, manic-like profile seen throug-

hout the day subsequent to a phase of calm at night. Mood oscillations corresponded to atypical daytime rises in VTA dopaminergic neuronal firing, tyrosine hydroxylase (TH) activity and dopamine biosynthesis. The investigators created a novel optogenetic stimulation prototype in wild type (WT) mice, in which the genetically unaltered strains were photo-stimulated (ventral tegmental area only) in a chronic fashion for 7 consecutive days (1 hr/d) followed by behavioral and physiological measurements. The WT mice exhibited same rapid cycling behavioral profile as *Clock△19* strains and this phenotype persevered for up to 2 weeks after termination of optic stimulation. Further, time-dependent inhibition of *TH* activity by alpha-methyl-para-tyrosine during the day reversed manic-like behaviors in both types of experimental animals. Moreover, it was demonstrated that the CLOCK protein was a negative regulator of TH gene transcription, disclosing an original molecular mechanistic link between the circadian apparatus and mood switching, and shedding light on the pathogenesis of
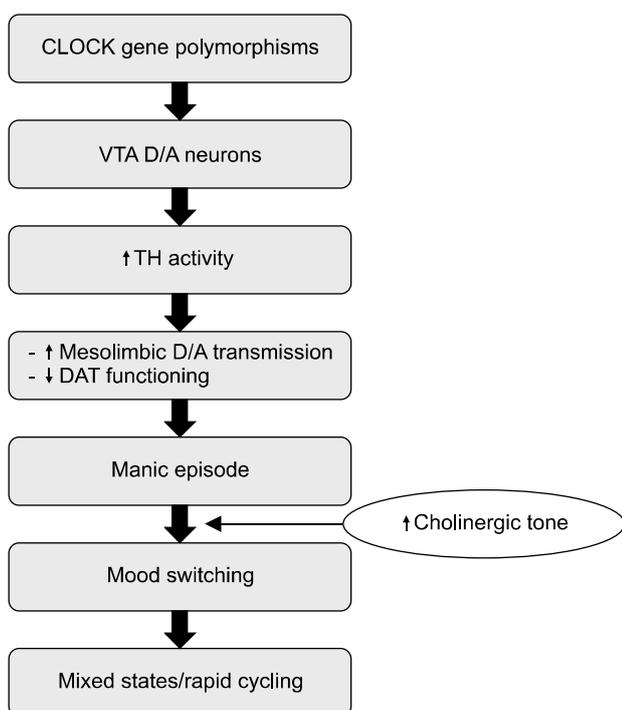
mood alterations in BD.[44]

The emerging evidence with respect to the pathogenesis of mood switching and induction of mixed symptoms in BD is schematically depicted in Fig. 4.

TREATMENT OF MIXED STATES

The occurrence of mixed symptoms in BD is a common phenomenon and an estimated 1/3 to 1/2 of suffers may be effected in this manner.[45] These cases tend to have repeated episodes with poor symptomatic and functional recovery. They often have comorbid anxiety and substance use disorders which further complicate the illness course and result in treatment refractoriness to currently available psychopharmacological agents.[46] Episodes with psychotic features may be more common, while the presence of sub-syndromal inter-episode symptoms and rapid cycling worsens the prognosis.[47] Suicide attempts are frequent in this group of patients, and there is a greater incidence of completed suicide in those bipolar sufferers experiencing mixed features.[48] While evaluating a patient, the clinician must be alert to the existence of mixed presentations as these generally indicate a more severe illness trajectory, poor treatment response, and a worse outcome.[49] The pharmacological agents employed in the therapy of mixed episodes are primarily atypical antipsychotics and mood stabilizers, including newer anticonvulsants.[50] No single agent is effective in controlling the manifestations of mixed states and

FIG. 4. Unifying hypothesis of mood switching and mixed states in bipolar disorder. In bipolar disorder, circadian rhythm perturbations play a key role. To date, several polymorphisms in the circadian apparatus genes have been identified. Now a mechanistic link has been proposed which involves mesolimbic dopamine transmission. Mutations in *Clock* genes lead to a hyperdopaminergic state and precipitation of manic episodes. Polymorphisms in the dopamine transporter (DAT) gene further contribute to this disturbance. Mood switching is secondary to an imbalance in cholinergic neurotransmission, with decreased functioning of acetylcholinesterase and increased synaptic acetylcholine. This induces depressive symptoms, and gives rise to mixed states and rapid cycling. D/A: dopamine, TH: tyrosine hydroxylase, VTA: ventral tegmental area.
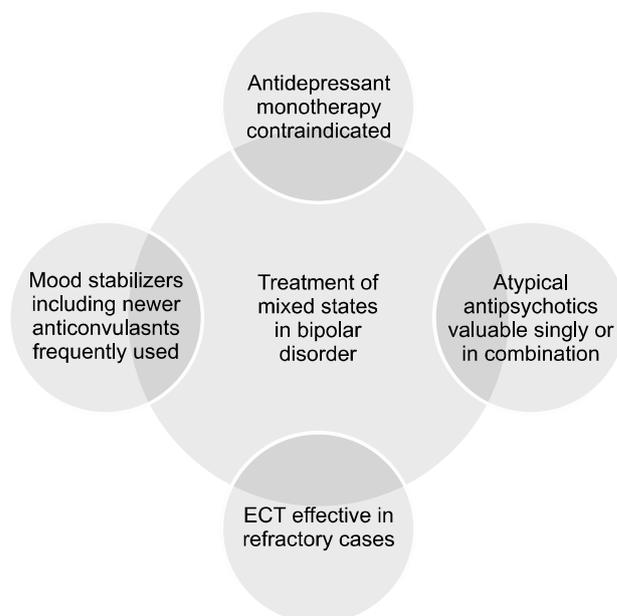

FIG. 5. The contemporary perspective of the treatment of mixed states in bipolar disorder. Mixed states are difficult to treat and no single agent is effective on its own, so that a combination of medications is often employed. Among the first line drugs are 2nd and 3rd generation antipsychotics, used alone or in conjunction with classical mood stabilizers. In this respect newer anticonvulsants show a favorable profile with good safety and efficacy parameters. Electroconvulsive therapy is an option in refractory cases.

combination treatment with two or more medications is the rule rather than the exception. Consequently, polypharmacy is common and there is a higher incidence of untoward medication side effects resulting in poor compliance from the patients.[51] In severe episodes with unsatisfactory response to psychopharmacological agents, electroconvulsive therapy (ECT) is an alternative strategy that is often rapidly effective and leads to the resolution of otherwise intractable symptoms.[52] The current understanding of the treatment of mixed states is illustrated in Fig. 5.

The next sections of the manuscript review the evidence with respect to 2nd and 3rd generation antipsychotics, mood stabilizers including newer anticonvulsants and ECT in the management of mixed states in BD.

1. Atypical antipsychotics

1) Risperidone: No randomized controlled trials (RCT) of risperidone in bipolar subjects with mixed symptomatology were found in the extant literature. However, an open label study of risperidone adjunctively to mood stabilizers, shed light on its usefulness in this group of patients. Forty cases of BD type I, current episode mixed, were administered adjunctive risperidone and followed for 20 weeks. Efficacy parameters were defined using the Young Mania Rating Scale (YMRS), Montgomery Asberg Depression Rating Scale (MADRS) and Global Assessment Scale. Repeated measures during the study period showed that non-blinded use of add-on risperidone was more efficacious in reducing manic as compared to depressive symptoms in patients experiencing DSM-IV-TR mixed episodes.[53] In another open label study, risperidone long acting injectable (RLAI) was administered every 2 weeks (dose: 25-50 mg) for 3 months to bipolar patients who had rapid cycling and continued to suffer from affective symptoms in spite of typically optimal treatment with other psychotropic medications. The sub-group of subjects with mixed symptoms (defined as YMRS ≥ 16 and any MADRS score) had significant improvement at the endpoint using the YMRS and the Clinical Global Impressions of Bipolar Disorder-Severity (CGI-BP-S).[54]

2) Olanzapine: In a pooled analysis from 3 previously conducted RCTs of olanzapine monotherapy versus placebo in acute manic or mixed episodes, DSM-5 criteria were employed to study sub-populations of BD type I patients experiencing "mania with mixed features". The Hamilton Rating Scale for Depression (HRSD-17) was utilized to sub-categorize the subjects and the YMRS was the primary efficacy measure. The post hoc analysis showed that at the study endpoint of week-3, the active drug was significantly better than placebo in treating manic episodes with or without mixed features. Further, olanzapine was more efficacious in those subjects with mixed symptoms who had a greater number of depressive features.[55]

3) Quetiapine: This drug is endorsed by the FDA for manic, depressive and maintenance phases of BD. Its effectiveness in the continued treatment and prevention of mixed episodes was demonstrated in a post hoc analysis of 2 main-

tenance phase studies that used quetiapine or placebo adjunctive to classical mood stabilizers lithium or divalproex sodium for a period of 104 weeks. It was revealed that while receiving quetiapine + lithium/divalproex as compared to placebo + mood stabilizer, patients with index mixed episodes (DSM-IV-TR) had fewer relapses of the same symptomatology; moreover, cases with any type of initial episodes experienced fewer mixed recurrences.[56] In the absence of data from acute phase studies, it can be assumed that quetiapine has value in the therapy of mixed states in BD.[57]

4) Ziprasidone: The extant literature is helpful in delineating the place of ziprasidone in acute manic and mixed episodes of BD type I, as well as its role as an adjunctive maintenance drug in stabilized patients. Data from short term 3 week RCTs is supportive of its efficacy as monotherapy in the acute treatment of psychotic or nonpsychotic manic and mixed episodes. In two 1-year open label extension studies, ziprasidone showed valid efficacy in the prevention of manic and mixed episodes adjunctive to mood stabilizers.[58] In a more recently published RCT, MDD patients with features suggestive of bipolarity (on the "bipolar spectrum") were either treated with ziprasidone alone or in conjunction with antidepressants. In comparison with placebo, the ziprasidone group was not statistically superior on the primary efficacy measure of MADRS, indicating that "mixed depression" may not be treatment responsive to this agent.[59]

5) Asenapine: This is a unique 2nd generation antipsychotic with a sub-lingual route of administration, having a pharmacodynamic effect on several dopaminergic and serotonergic receptors. Data from RCTs is obtainable for the management of bipolar patients in the acute and maintenance phases. In short-term monotherapy trials, asenapine was better than placebo in manic and mixed episodes with evidence of efficacy for depressive symptoms in mixed states. In maintenance phase studies, it showed similar efficacy to the well-known medication olanzapine in controlling the manic and depressive manifestations of BD.[60] In the long-term management of bipolar patients experiencing mixed episodes, a cost-effectiveness study showed that asenapine was superior to olanzapine as measured by quality-adjusted life years; increased cost for acquisition of asenapine was offset by earlier and sustained improvement in psychopathological symptoms and the functional domain with this agent.[61]

6) Lurasidone: This atypical antipsychotic is approved for the treatment of acute bipolar I depression and a recently published post-hoc analysis of an RCT sheds light on its utility in patients with three or more manic symptoms accompanying the MDE. Subjects with YMRS scores ≥ 4 at baseline were considered as having bipolar depression with mixed features and when administered the active agent as compared to placebo they showed significant reductions in MADRS, the primary efficacy measure. Rates of treatment emergent switching to mania or hypomania were similar in the groups with or without mixed features and comparable to placebo.[62]

7) Aripiprazole: This 3rd generation antipsychotic exhibits the pharmacodynamic properties of partial agonism and functional selectivity at the dopamine D$_2$ receptor, as well as serotonin-dopamine activity modulation. It is highly efficacious in schizophrenia, schizoaffective disorder and BD. Short term RCTs demonstrated its value in acute manic and mixed episodes, whereas long term maintenance trials have shown that aripiprazole is effective in relapse prevention in patients with recurrent manic and mixed episodes. Overall, evidence from controlled studies is supportive of this medication's efficacy in bipolar subjects afflicted by mixed states; with the added advantage that aripiprazole has a favorable safety and tolerability profile.[63]

2. Mood stabilizers

1) Lithium: This classical mood stabilizer is an inhibitor of glycogen synthase kinase 3β, which may underlie its therapeutic action in BD. In so far as management of mixed states is concerned, evidence shows that lithium has value in the treatment of classic euphoric mania, while dysphoric mania is poorly responsive to this agent. The contemporary perspective dictates that lithium is most useful in acute, purely manic episodes as standalone therapy or adjunctively with atypical antipsychotics, while it has value as a maintenance agent in patients with manic polarity of illness.[64]

2) Divalproex sodium: Valproate is a histone deacetylase inhibitor, an action which may result in therapeutic value in BD. The existing literature supports its efficacy in dysphoric mania, rapid cycling, and bipolar depression as monotherapy or adjunctively to a new generation antipsychotic. It can be used in acute episodes as well as prophylactically, with the caveat that careful attention is needed in individual cases as this medication has myriad adverse effects including neurologic, hematologic, metabolic, endocrine, and teratogenic effects.[65]

3) Carbamazepine/oxcarbazepine/eslicarbazepine: These structurally related compounds are primarily used as anticonvulsants, but have established a niche in the treatment of mood disorders. Carbamazepine is now most often used in an extended-release (ER) formulation, which has been studied in adults with BD type I in at least two RCTs. A pooled, post hoc analysis revealed that carbamazepine ER was superior to placebo in treating manic symptoms, while a sub-group analysis demonstrated that it had valid efficacy in mixed states as measured by YMRS and HRSD.[66]

Oxcarbazepine is the keto derivative of carbamazepine and may offer pharmacokinetic advantages over the parent compound. A systematic review of the literature showed that there was a paucity of adequately powered RCTs to inform about the efficacy of oxcarbazepine in acute episodes in BD. Studies mainly investigated the treatment of mania, whereas there were statistics from sub-analysis on mixed states, rapid cycling and hypomania. Compared to placebo, this medication was efficacious in acute manic and mixed episodes, but did not differ from active comparators like lithium or valproate on efficacy measures. Good quality data on patient and clinician related outcomes and safety and tolerability were not forthcoming, pointing to the need for suitably conducted trials of proper methodology.[67]

Eslicarbazepine is an active metabolite of oxcarbazepine and has been studied in bipolar disorder. Only one RCT was identified during the literature search which was conducted in bipolar patients with acute manic episodes. In the short term (3 weeks), eslicarbazepine was no different from placebo on YMRS, the primary efficacy parameter. In the long term (up to 6 months) it showed some efficacy in preventing acute episodes and reducing overall affective symptomatology, as determined by primary and secondary (CGI-BP) measures. In these trials, eslicarbazepine had a good safety and tolerability profile.[68] At this stage more studies are needed to delineate the place of this 3rd generation anticonvulsant in the treatment of BD.

4) Lamotrigine: Introduced as an anticonvulsant, this medication was extensively studied in BD. A summation of the evidence from controlled trials leads to the following conclusions:[69]

(1) There is lack of proof of the effectiveness in acute manic and mixed episodes in monotherapy trials.

(2) Some data support its usefulness in acute bipolar depression, but this effect is limited to milder presentations.

(3) In the long-term treatment of BD, lamotrigine is not efficacious in the prophylaxis of manic or mixed recurrences.

(4) It appears to have valid efficacy as a maintenance agent in bipolar subjects suffering from predominantly depressive recurrences.

(5) It is not an effective treatment for rapid cycling.

(6) Lamotrigine's use in BD is not associated with manic switching or induction of mixed episodes.

5) Topiramate: This novel anticonvulsant is unique as its use is associated with weight reduction, so that it is an appealing treatment option in BD subjects with raised body mass index, as well as in children and adolescents afflicted by this ailment. While randomized controlled trials do not endorse its efficacy in acute manic or mixed episodes, data from open label studies is more supportive of topiramate's role in BD. One such study employed topiramate with olanzapine in bipolar subjects with mixed symptomatology for up to 1 year. The combination was well tolerated and the patients showed significant improvement on key efficacy measures like the YMRS, HRSD and CGI-BP. Additionally, the weight gaining effect of olanzapine was apparently countered by adjunctive topiramate, with a net weight reduction of 0.5 kg in cases who completed the 1 year study period.[70]

6) Gabapentin/pregabalin: Developed as antiepileptics, the gabapentinoids are often employed for the alleviation of neuropathic pain. These medications have been studied in affective disorders, and although controlled trials are not supportive of their role in BD, open label studies point to their usefulness in bipolar spectrum disorders. The following observations are made after examining the extant

literature:[71]

   (1) Gabapentinoids are an option in refractory cases.

   (2) These may be particularly useful in bipolar subjects suffering from comorbid anxiety spectrum disorders.

   (3) These may be considered as second line agents in subjects with rapid cycling, mixed states and sub-threshold affective symptoms.

   (4) These have valid efficacy in substance use disorders, particularly alcohol spectrum disorders which are frequently comorbid with BD.

   (5) Bipolar patients with neurological conditions like neuropathic pain, migraine, restless legs syndrome and dizziness may benefit from these agents.

   (6) Last but not the least, these have a favorable pharmacokinetic profile with good safety and tolerability to validate their use in BD.

3. Electroconvulsive therapy (ECT)

There are an increasing number of studies on the application of different cerebral stimulation techniques in the treatment of mood disorders. These include ECT, repetitive transcranial magnetic stimulation, vagus nerve stimulation, and deep brain stimulation. With regards to effectiveness, the existing literature is most supportive of ECT which emerges as a rapidly effective measure in intractable cases who are not showing response to manipulation with existing psychopharmacological agents. ECT is a valid treatment option in actively suicidal patients, catatonic cases, subjects with refractory mixed states and those exhibiting persistent, severe affective symptomatology poorly responsive to pharmacotherapy.[72] Table 2 provides a summary of effectiveness of treatment measures on mixed mood states in bipolar disorder.

CONCLUSIONS

In this review an effort has been made to highlight the clinical burden of mixed affective symptoms in BD, with

TABLE 2. Efficacy of biological treatment strategies for mixed states in bipolar disorder

Atypical antipsychotics	Effect on manic symptoms	Effect on depressive symptoms	Relapse prevention (mixed episodes)	Comments
Risperidone	+	±	+	Manic symptoms more responsive. RCT evidence equivocal for depressive manifestations.
Paliperidone	+	−	+	Paliperidone palmitate efficacious in schizoaffective disorder.
Olanzapine	+	+	+	Best evidence for DSM-5 "with mixed features" specifier.
Quetiapine	+	±	+	Effective in all phases of BD.
Ziprasidone	+	±	−	"Mixed depression" poorly responsive.
Asenapine	+	±	±	Similar efficacy to olanzapine, with better cost-effectiveness.
Aripiprazole	+	−	+	Consistently more effective for manic than depressive symptoms.
Classical MS				
Lithium	−	−	−	Poor evidence of efficacy in mixed episodes.
Valproate	+	+	−	Efficacious in acute mixed episodes/RC/bipolar depression.
Carbamazepine	±	±	±	Evidence equivocal with respect to mixed episodes.
Lamotrigine	−	±	±	Best evidence as maintenance agent (depressive polarity).
Combination treatment				
Valproate + olanzapine	+	+	+	Mixed episodes respond well to the combination strategy.
Lithium + olanzapine	+	±	±	Manic symptoms better responsive than depressive symptoms.
Lithium/valproate + quetiapine	±	±	+	Good evidence for prevention of mixed episodes.
Lithium/valproate + aripiprazole	+	+	±	Efficacy against manic/depressive symptoms of acute mixed episodes.
ECT	+	+	±	Effective in acute mixed episodes.

BD: bipolar disorder, DSM-5: diagnostic and statistical manual 5th edition, ECT: electroconvulsive therapy, MS: mood stabilizers, RC: rapid cycling, RCT: randomized controlled trial.

particular reference to the broadening of the concept enshrined in DSM-5. Currently, the "mixed features" specifier can be applied to manic, hypomanic, and depressive episodes in both the bipolar spectrum and major depressive disorders. Therefore, with this paradigm shift many more mood disorder patients would be diagnosed with mixed states. In this scenario there is an overwhelming need to understand the neurobiological underpinnings of mixed states and the related phenomena of mood switching and rapid cycling. To fulfill this requirement, the current theorization involving circadian genes, neurotransmitters and fluctuations in affective states is presented. While the catecholamine-acetylcholine imbalance remains a hypothesis, emerging evidence is increasingly supportive of the contemporary premise and further elucidation of the underlying mechanisms that may result in important insights into the pathophysiology of bipolar disorder. Whereas, current treatment methods are mainly palliative, new knowledge can lead to an improved understanding and better and more effective therapies for sufferers with the bipolar diathesis.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Trede K, Salvatore P, Baethge C, Gerhard A, Maggini C, Baldessarini RJ. Manic-depressive illness: evolution in Kraepelin's textbook, 1883-1926. Harv Rev Psychiatry 2005;13:155-78.

2. Verdolini N, Agius M, Ferranti L, Moretti P, Piselli M, Quartesan R. The state of the art of the DSM-5 "with mixed features" specifier. ScientificWorldJournal 2015;2015:757258.

3. McIntyre RS, Soczynska JK, Cha DS, Woldeyohannes HO, Dale RS, Alsuwaidan MT, et al. The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and bipolar disorder: results from the International Mood Disorders Collaborative Project. J Affect Disord 2015;172:259-64.

4. Vieta E, Valentí M. Mixed states in DSM-5: implications for clinical care, education, and research. J Affect Disord 2013;148:28-36.

5. Shim IH, Woo YS, Bahk WM. Prevalence rates and clinical implications of bipolar disorder "with mixed features" as defined by DSM-5. J Affect Disord 2015;173:120-5.

6. Fagiolini A, Coluccia A, Maina G, Forgione RN, Goracci A, Cuomo A, et al. Diagnosis, epidemiology and management of mixed states in bipolar disorder. CNS Drugs 2015;29:725-40.

7. Tundo A, Musetti L, Benedetti A, Berti B, Massimetti G, Dell'Osso L. Onset polarity and illness course in bipolar I and II disorders: the predictive role of broadly defined mixed states. Compr Psychiatry 2015;63:15-21.

8. Palma M, Ferreira B, Borja-Santos N, Trancas B, Monteiro C, Cardoso G. Efficacy of electroconvulsive therapy in bipolar disorder with mixed features. Depress Res Treat 2016;2016:8306071.

9. Muneer A. Staging models in bipolar disorder: a systematic review of the literature. Clin Psychopharmacol Neurosci 2016;14:117-30.

10. Fornaro M, De Berardis D, Koshy AS, Perna G, Valchera A, Vancampfort D, et al. Prevalence and clinical features associated with bipolar disorder polypharmacy: a systematic review. Neuropsychiatr Dis Treat 2016;12:719-35.

11. Smolensky MH, Hermida RC, Reinberg A, Sackett-Lundeen L, Portaluppi F. Circadian disruption: New clinical perspective of disease pathology and basis for chronotherapeutic intervention. Chronobiol Int 2016;33:1101-19.

12. Bechtel W. Circadian rhythms and mood disorders: are the phenomena and mechanisms causally related? Front Psychiatry 2015;6:118.

13. Wang B, Chen D. Evidence for seasonal mania: a review. J Psychiatr Pract 2013;19:301-8.

14. Milhiet V, Boudebesse C, Bellivier F, Drouot X, Henry C, Leboyer M, et al. Circadian abnormalities as markers of susceptibility in bipolar disorders. Front Biosci (Schol Ed) 2014;6:120-37.

15. Moreira J, Geoffroy PA. Lithium and bipolar disorder: impacts from molecular to behavioural circadian rhythms. Chronobiol Int 2016;33:351-73.

16. Lee HJ, Son GH, Geum D. Circadian rhythm hypotheses of mixed features, antidepressant treatment resistance, and manic switching in bipolar disorder. Psychiatry Investig 2013;10:225-32.

17. Gustafson CL, Partch CL. Emerging models for the molecular basis of mammalian circadian timing. Biochemistry 2015;54:134-49.

18. Landgraf D, McCarthy MJ, Welsh DK. Circadian clock and stress interactions in the molecular biology of psychiatric disorders. Curr Psychiatry Rep 2014;16:483.

19. Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R. Rapid cycling bipolar disorder--diagnostic concepts. Bipolar Disord 2008;10:153-62.

20. Young JW, Dulcis D. Investigating the mechanism(s) underlying switching between states in bipolar disorder. Eur J Pharmacol 2015;759:151-62.

21. Koszewska I, Rybakowski JK. Antidepressant-induced mood conversions in bipolar disorder: a retrospective study of tricyclic versus non-tricyclic antidepressant drugs. Neuropsychobiology 2009;59:12-6.

22. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006;163:232-9.

23. Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006;189:124-31.

24. Santangelo G, Barone P, Trojano L, Vitale C. Pathological gambling in Parkinson's disease. A comprehensive review. Parkinsonism Relat Disord 2013;19:645-53.

25. Vaughan RA, Foster JD. Mechanisms of dopamine transporter regulation in normal and disease states. Trends Pharmacol Sci 2013;34:489-96.

26. van Enkhuizen J, Janowsky DS, Olivier B, Minassian A, Perry W, Young JW, et al. The catecholaminergic-cholinergic balance hypothesis of bipolar disorder revisited. Eur J Pharmacol 2015;753:114-26.

27. Anand A, Darnell A, Miller HL, Berman RM, Cappiello A, Oren

DA, et al. Effect of catecholamine depletion on lithium-induced long-term remission of bipolar disorder. Biol Psychiatry 1999; 45:972-8.

28. Hannestad JO, Cosgrove KP, DellaGioia NF, Perkins E, Bois F, Bhagwagar Z, et al. Changes in the cholinergic system between bipolar depression and euthymia as measured with [123I]5IA single photon emission computed tomography. Biol Psychiatry 2013;74:768-76.

29. Saricicek A, Esterlis I, Maloney KH, Mineur YS, Ruf BM, Muralidharan A, et al. Persistent β2*-nicotinic acetylcholinergic receptor dysfunction in major depressive disorder. Am J Psychiatry 2012;169:851-9.

30. McIntyre RS, Cha DS, Kim RD, Mansur RB. A review of FDA-approved treatment options in bipolar depression. CNS Spectr 2013;18 Suppl 1:4-20.

31. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 2015;45:693-704.

32. van Enkhuizen J, Minassian A, Young JW. Further evidence for Clock△19 mice as a model for bipolar disorder mania using cross-species tests of exploration and sensorimotor gating. Behav Brain Res 2013;249:44-54.

33. Abreu T, Bragança M. The bipolarity of light and dark: a review on bipolar disorder and circadian cycles. J Affect Disord 2015;185:219-29.

34. Levenson JC, Wallace ML, Anderson BP, Kupfer DJ, Frank E. Social rhythm disrupting events increase the risk of recurrence among individuals with bipolar disorder. Bipolar Disord 2015;17:869-79.

35. Akhter A, Fiedorowicz JG, Zhang T, Potash JB, Cavanaugh J, Solomon DA, et al. Seasonal variation of manic and depressive symptoms in bipolar disorder. Bipolar Disord 2013;15:377-84.

36. Sit D, Wisner KL, Hanusa BH, Stull S, Terman M. Light therapy for bipolar disorder: a case series in women. Bipolar Disord 2007;9:918-27.

37. Geoffroy PA, Bellivier F, Scott J, Etain B. Seasonality and bipolar disorder: a systematic review, from admission rates to seasonality of symptoms. J Affect Disord 2014;168:210-23.

38. Lee HJ, Woo HG, Greenwood TA, Kripke DF, Kelsoe JR. A genome-wide association study of seasonal pattern mania identifies NF1A as a possible susceptibility gene for bipolar disorder. J Affect Disord 2013;145:200-7.

39. Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, et al. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 2006;141B:234-41.

40. McClung CA. How might circadian rhythms control mood? Let me count the ways. Biol Psychiatry 2013;74:242-9.

41. Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, et al. Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci U S A 2007;104:6406-11.

42. Del'Guidice T, Latapy C, Rampino A, Khlghatyan J, Lemasson M, Gelao B, et al. FXR1P is a GSK3β substrate regulating mood and emotion processing. Proc Natl Acad Sci U S A 2015; 112:E4610-9.

43. Mukherjee S, Coque L, Cao JL, Kumar J, Chakravarty S, Asaithamby A, et al. Knockdown of Clock in the ventral tegmental area through RNA interference results in a mixed state of mania and depression-like behavior. Biol Psychiatry 2010;68:503-11.

44. Sidor MM, Spencer SM, Dzirasa K, Parekh PK, Tye KM, Warden MR, et al. Daytime spikes in dopaminergic activity drive rapid mood-cycling in mice. Mol Psychiatry 2015;20:1406-19.

45. Clemente AS, Diniz BS, Nicolato R, Kapczinski FP, Soares JC, Firmo JO, et al. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. Rev Bras Psiquiatr 2015; 37:155-61.

46. Muneer A. Pharmacotherapy of acute bipolar depression in adults: an evidence based approach. Korean J Fam Med 2016;37:137-48.

47. Ostergaard SD, Bertelsen A, Nielsen J, Mors O, Petrides G. The association between psychotic mania, psychotic depression and mixed affective episodes among 14,529 patients with bipolar disorder. J Affect Disord 2013;147:44-50.

48. Seo HJ, Wang HR, Jun TY, Woo YS, Bahk WM. Factors related to suicidal behavior in patients with bipolar disorder: the effect of mixed features on suicidality. Gen Hosp Psychiatry 2016; 39:91-6.

49. Carvalho AF, Dimellis D, Gonda X, Vieta E, McIntyre RS, Fountoulakis KN. Rapid cycling in bipolar disorder: a systematic review. J Clin Psychiatry 2014;75:e578-86.

50. Fornaro M, Stubbs B, De Berardis D, Perna G, Valchera A, Veronese N, et al. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials. Int J Mol Sci 2016;17:241.

51. Chue P, Chue J. A critical appraisal of paliperidone long-acting injection in the treatment of schizoaffective disorder. Ther Clin Risk Manag 2016;12:109-16.

52. Devanand DP, Polanco P, Cruz R, Shah S, Paykina N, Singh K, et al. The efficacy of ECT in mixed affective states. J ECT 2000;16:32-7.

53. Singh V, Bowden CL, Mintz J. Relative effectiveness of adjunctive risperidone on manic and depressive symptoms in mixed mania. Int Clin Psychopharmacol 2013;28:91-5.

54. Macfadden W, Adler CM, Turkoz I, Haskins JT, Turner N, Alphs L. Adjunctive long-acting risperidone in patients with bipolar disorder who relapse frequently and have active mood symptoms. BMC Psychiatry 2011;11:171.

55. Tohen M, McIntyre RS, Kanba S, Fujikoshi S, Katagiri H. Efficacy of olanzapine in the treatment of bipolar mania with mixed features defined by DSM-5. J Affect Disord 2014;168:136-41.

56. Vieta E, Suppes T, Ekholm B, Udd M, Gustafsson U. Long-term efficacy of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder. J Affect Disord 2012;142:36-44.

57. Muneer A. Pharmacotherapy of bipolar disorder with quetiapine: a recent literature review and an update. Clin Psychopharmacol Neurosci 2015;13:25-35.

58. Warrington L, Lombardo I, Loebel A, Ice K. Ziprasidone for the treatment of acute manic or mixed episodes associated with bipolar disorder. CNS Drugs 2007;21:835-49.

59. Patkar AA, Pae CU, Vöhringer PA, Mauer S, Narasimhan M, Dalley S, et al. A 13-week, randomized double-blind, placebo-con-

trolled, cross-over trial of ziprasidone in bipolar spectrum disorder. J Clin Psychopharmacol 2015;35:319-23.

60. Vita A, De Peri L, Siracusano A, Sacchetti E; ATOM Group. Efficacy and tolerability of asenapine for acute mania in bipolar I disorder: meta-analyses of randomized-controlled trials. Int Clin Psychopharmacol 2013;28:219-27.

61. Sawyer L, Azorin JM, Chang S, Rinciog C, Guiraud-Diawara A, Marre C, et al. Cost-effectiveness of asenapine in the treatment of bipolar I disorder patients with mixed episodes. J Med Econ 2014;17:508-19.

62. McIntyre RS, Cucchiaro J, Pikalov A, Kroger H, Loebel A. Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. J Clin Psychiatry 2015; 76:398-405.

63. Muneer A. The treatment of adult bipolar disorder with aripiprazole: a systematic review. Cureus 2016;8:e562.

64. Ketter TA, Miller S, Dell'Osso B, Wang PW. Treatment of bipolar disorder: Review of evidence regarding quetiapine and lithium. J Affect Disord 2016;191:256-73.

65. Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev 2013;(10):CD003196.

66. Weisler RH, Hirschfeld R, Cutler AJ, Gazda T, Ketter TA, Keck PE, et al. Extended-release carbamazepine capsules as monotherapy in bipolar disorder: pooled results from two randomised, double-blind, placebo-controlled trials. CNS Drugs 2006;20:219-31.

67. Vasudev A, Macritchie K, Vasudev K, Watson S, Geddes J, Young AH. Oxcarbazepine for acute affective episodes in bipolar disorder. Cochrane Database Syst Rev 2011;(12):CD004857.

68. Grunze H, Kotlik E, Costa R, Nunes T, Falcão A, Almeida L, et al. Assessment of the efficacy and safety of eslicarbazepine acetate in acute mania and prevention of recurrence: experience from multicentre, double-blind, randomised phase II clinical studies in patients with bipolar disorder I. J Affect Disord 2015;174:70-82.

69. Amann B, Born C, Crespo JM, Pomarol-Clotet E, McKenna P. Lamotrigine: when and where does it act in affective disorders? A systematic review. J Psychopharmacol 2011;25:1289-94.

70. Vieta E, Sánchez-Moreno J, Goikolea JM, Colom F, Martínez-Arán A, Benabarre A, et al. Effects on weight and outcome of long-term olanzapine-topiramate combination treatment in bipolar disorder. J Clin Psychopharmacol 2004;24:374-8.

71. Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? Epilepsia 2012;53 Suppl 7:26-33.

72. Medda P, Toni C, Perugi G. The mood-stabilizing effects of electroconvulsive therapy. J ECT 2014;30:275-82.