Section A: Bipolar depression: Clinical phenotype and course of illness

Summary
Andreas Marneros
The history of bipolar disorders

Bipolar disorders have a long history. Depression and mania are mankind’s oldest known mental disorders, and they were the first mental disorders conceptualised by Hippocrates as a part of medicine. Mania and depression as part of one and the same disease – what we today call bipolar disorder – was first described by the famous Greek physician of the first Century AD, Aretaeus of Cappadocia.

The next decisive step in the development of our conceptualisation of bipolar disorders was done by two French psychiatrists, Falret (1851) and Baillarger (1854), who described them as separate entities. At the end of the 19th Century, Emil Kraepelin subsumed all kinds of mood disorders – both unipolar and bipolar – under the umbrella of manic-depressive insanity. But there was also strong opposition against the very influential opinions of Kraepelin, especially by the so-called Wernicke-Kleist-Leonhard school (Karl Kleist coined the term ‘bipolar’), which subclassified bipolar disorders into distinct entities. In 1966, Angst and Perris showed that unipolar and bipolar disorders are autonomous. That was also the start of a very rapid development of concepts, research, and general knowledge about bipolar disorders.

Subgroups like cyclothymia, hypomania, and mixed states were identified or re-identified. Another innovation was the development of a bipolar spectrum disorder concept. An overlap of bipolar and schizophrenic spectra can be postulated which is certainly genetically determined, and which gives rise to states like bipolar schizoaffective disorders or acute polymorphic disorders.

Keywords: bipolar disorder, history, bipolar spectrum, overlap of spectra, Hippocrates, Aretaeus of Cappadocia, bipolar II, cyclothymia, hypomania, mixed states, bipolar schizoaffective, rapid cycling, acute and transient psychotic disorders

Summary
Gordon B. Parker and Kathryn Fletcher
The clinical diagnosis of bipolar depression

‘Bipolar depression’ is not a specific type of depression, with most episodes phenotypically weighted to melancholic or psychotic depression. In order to improve our understanding of the etiology and management of bipolar depression, sub-typing heterogeneity should be constrained. A ‘top-down’ approach to delineate specific sub-typing characteristics is suggested, allowing consideration as to whether ‘bipolar depression’ differs in expression across bipolar I (BPD I) and II (BPD II) disorders. Current diagnostic systems employ imprecise criteria to differentiate sub-types of BPD, disallowing ‘top-down’ studies seeking to identify prototypical bipolar depression features.

We describe a categorical ‘isomer’ model, assisting discrimination between bipolar sub-types and unipolar depressive disorders. In essence, the respective presence or absence of psychotic features differentiates BPD I from BPD II, with a core elevated mood/energy construct delineating BPD from unipolar disorders. Our model allows a ‘top-down’ approach to clinical diagnosis, versus the questionable validity of the bipolar spectrum ‘soft signs’ approach.
Keywords: bipolar disorder (BPD), depression, diagnosis, sub-type, atypical, model, spectrum, characteristic, melancholic, psychotic

Summary
Tamas Treuer and Mauricio Tohen
Course and outcome of bipolar disorder – focusing on depressive aspects

The prognosis of an illness is perhaps relatively more valuable in psychiatry than in other therapeutic areas, because the lack of a laboratory-based diagnostic test and poor biological markers in mental disorders limit outcome predictions based mostly on the information from the psychiatric interview and examination. This is particularly true in bipolar disorder. In this chapter the authors summarize the main factors predicting course and outcome in bipolar disorder with a focus on depressive symptoms. The natural course, the impact of first episode, the impact of depressive phase, cycle length, onset, age, gender, type of illness, personality traits and temperament, co-morbidity, family history, life events, and outcome features will be reviewed. Conceptual models and their prognostic value will be discussed as well.

Keywords: bipolar disorder, course, outcome, prognosis, depressive aspects, predictors, clinical assessment, bipolar depression, mixed depression, mania, clinical diagnosis, rapid cycling, functional recovery

Summary
Zoltán Rihmer
Suicide and bipolar disorder

Bipolar disorders are common illnesses with markedly elevated premature mortality, but they remain frequently under-referred, under-diagnosed, and under-treated. Suicide is the cause of death in up to 15% of patients with bipolar disorders, and about half of them make at least one suicide attempt in their lifetime. The suicide rate of (untreated) bipolar patients is 25 times higher than the same rate in the general population. Suicidal behaviour in bipolar patients occurs almost exclusively during severe major depressive episodes, and less frequently in mixed affective episodes or in dysphoric mania. In contrast, suicidal behaviour occurs very rarely during euphoric mania, hypomania, or euthymia, suggesting that suicidal behaviour in bipolar patients is a state- and severity-dependent phenomenon. However, because the majority of bipolar patients never commit (and up to 50% of them never attempt) suicide, risk factors other than bipolar disorder itself also play a significant contributory role. This chapter summarises the clinically most relevant suicide risk and protective factors in bipolar disorders, and touches briefly on the most effective suicide prevention strategies.

Keywords: bipolar disorder, unipolar depression, major depressive episode, suicide, suicide attempt, suicidal ideation, suicide risk factors, suicide protective factors, suicide prevention

Section B: Bipolar depression: Neurobiology

Summary
Thomas G. Schulze and Francis J. McMahon
The genetic basis of bipolar disorder

Bipolar disorder has long been known to have a strong genetic component, with heritability estimates ranging between 80–90%. However, major breakthroughs on the molecular genetic
level have remained elusive. Linkage and candidate gene association studies produced a host of reports, but failed to deliver consistently replicable results. This may in part be attributed to limited sample sizes and high degrees of phenotypic and genotypic heterogeneity. The advent of genome-wide association studies (GWAS) has spurred new hopes for the identification of true susceptibility genes. After close to a century of genetic studies, bipolar disorder is emerging as a complex (non-Mendelian) disorder with a polygenic etiology. The search for common genetic variants with small effects by GWAS will probably have to be complemented by approaches that can detect rare genetic variations with larger effects, such as copy number variants. Progress would be much enhanced by improved phenotype definitions that reduce genetic heterogeneity.

**Keywords:** bipolar disorder, schizophrenia, depression, psychosis, complex disorder, polygenic etiology, genome, linkage, association, reverse phenotyping, pharmacogenetics, SNP, CNV, GWAS

**Summary**

**Jun-Feng Wang and L. Trevor Young**

**Understanding the neurobiology of bipolar depression**

Many studies have shown decreased brain volume and cell number in prefrontal and limbic regions of bipolar disorder subjects, suggesting presence of disturbed neuronal circuitry and impaired neuroplasticity in these regions. The serotonin system plays an important role in depression and is a target of antidepressants. Studies have shown that the major serotonin metabolite 5-HIAA and serotonin transporter activity are decreased in cerebrospinal fluid, brain or platelets of subjects with bipolar depression, indicating that an abnormal serotonin system also contributes significantly to this disease. Mitochondria regulate synthesis, release and uptake of neurotransmitters via energy production. Evidence has shown that glucose metabolic rate and cerebral blood flow are decreased in bipolar depression. Studies also suggest defects in mitochondrial electron transport chain and oxidative damage in bipolar disorder. These studies together indicate that bipolar depression may be associated with an abnormal serotonin system resulting from mitochondrial dysfunction-induced impaired neuroplasticity in neuronal circuitry related to mood regulation.

**Key words:** Bipolar disorder, depression, neuroplasticity, serotonin metabolite, serotonin transporter, energy metabolism, glucose metabolic rate, cerebral blood flow, mitochondrial dysfunction, oxidative stress

**Summary**

**Wallace C. Duncan, Jr.**

**Non-pharmacological treatments and chronobiological aspects of bipolar disorder: implications for novel therapeutics**

This chapter reviews prominent neurobiological effects of chronotherapies for the treatment of mood disorders and integrates previously described therapeutic mechanisms with current advances regarding molecular signaling pathways and neuroplasticity. Scientific discoveries associated with circadian rhythms, disrupted sleep-wake patterns, and mood cycling, have establish preliminary links between circadian clock genes and mood. Importantly, the recent description of lithium’s effects on the molecular signaling pathways of the circadian system has advanced our understanding of the intracellular molecular bases of lithium’s mood stabilizing properties. Specifically discussed are the convergent intracellular pathways of monoaminergic drug therapies and chronotherapies (sleep deprivation (SD), light treatment
(LT), and sleep phase advance (SPA)), and the advantage of understanding their common pathways for developing novel therapeutic treatments.

**Keywords:** mood disorder, bipolar disorder, sleep deprivation, light therapy, dark therapy, phase-advance, antidepressants, lithium, clock genes, serotonin, dopamine

**Summary**

**Jonathan Savitz and Wayne C. Drevets**

**Neuroimaging studies of bipolar depression: therapeutic implications**

Bipolar disorder (BPD) is characterized by pathophysiological changes to the visceromotor network, disrupting the regulation of endocrine and autonomic responses to stress, and hence emotion and behavior. Specifically, reductions in gray matter volume and a concomitant increase in glutamatergic neurotransmission, is observed in the pregenual (pgACC) and subgenual anterior cingulate cortex (sgACC), the orbitofrontal, frontal polar and ventrolateral prefrontal cortex (PFC), the posterior cingulate, ventral striatum, and hippocampus. While increased glutamatergic signaling is equally salient in the amygdala, the data are conflicting on the nature of volumetric changes in this region. Neuroreceptor imaging data provide preliminary evidence for serotonin, serotonin transporter (5-HTT), dopamine receptor, and cholinergic system dysfunction in BPD. Oft-reported abnormalities of the deep frontal and basal ganglia white matter, and enlargement of the third and lateral ventricles are likely associated with cerebrovascular disease. Mood stabilizers and antidepressant drugs may attenuate pathological limbic activity, and increase neurotrophic processes, restoring balance to the system.

**Keywords:** bipolar disorder (BPD); major depressive disorder (MDD); MRI; neuroimaging; amygdala; hippocampus; basal ganglia; white matter hyperintensities (WMH); ventricles; subgenual prefrontal cortex; medial prefrontal cortex; dorsolateral prefrontal cortex; lateralization; genetics; imprinting

**Section C: Acute and long-term treatment of bipolar disorder**

**Gary S. Sachs, Louisa G. Sylvia and Hannah G. Lund**

**Pharmacological treatment of acute bipolar depression**

Acute depression is the condition for which bipolar patients most often seek treatment. The foundation of evidence-based practice is the practitioner’s obligation to inform the patient of proven therapies that may exist to treat their condition. The best guidance for meeting this obligation in clinical practice comes from double-blind, placebo-controlled trials with adequate sample size, referred to in this chapter as Category A evidence. This level of evidence is currently available for only four pharmacological treatments, lamotrigine, olanzapine plus fluoxetine, olanzapine monotherapy, and quetiapine. Interestingly, the most common treatment for bipolar depression – the adjunctive use of standard antidepressants along with lithium or valproate – has not been shown to be effective in any Category A study. Additional treatments for bipolar depression are needed for the many depressed bipolar patients who do not respond adequately to currently available treatments. Several classes of medications show promise for these patients. Exploring the variety of mechanisms by which these medications work may shed light on the pathophysiology of bipolar disorder.

**Keywords:** bipolar disorder, depression, Category A, lamotrigine, olanzapine plus fluoxetine, olanzapine, quetiapine, antidepressant, lithium, valproate, double-blind, placebo
The goal of pharmacological treatment of bipolar disorder is to prevent future occurrences of mood episodes. To achieve this goal, medications must demonstrate efficacy in the prevention of both manic/hypomanic and depressive relapses/recurrences. Currently, the efficacy of most pharmacological agents in the maintenance treatment of bipolar disorder has been studied using relapse prevention designs, in which only patients who tolerate and respond to a studied drug(s) in the acute phase (mania or depression) can enter the maintenance phase. Subsequently, the results from relapse prevention studies are not generalizable, not only because of the design, but also because of different index mood episodes. So far, however, only lithium and lamotrigine, and to some extent divalproex, have been investigated in both manic and depressive index episodes, while olanzapine and aripiprazole have been evaluated in manic index episodes. To facilitate the application of currently available data, this chapter will systematically examine randomized, blinded, controlled maintenance studies enrolling ≥ 100 patients and lasting ≥ 6 months.

**Keywords:** index episode, mania, bipolar depression, efficacy, prevention relapse design, enriched sample, maintenance, lithium, divalproex, lamotrigine, olanzapine, aripiprazole

Non-pharmacological somatic treatments have a long history in the care of patients with bipolar disorder. Indeed, electroconvulsive therapy (ECT) is the biological intervention with the longest history of continuous use in psychiatry, and it remains the most effective acute treatment available for either unipolar or bipolar depression or mania. This chapter discusses the therapeutic properties of ECT in the acute treatment of bipolar depression, mania, and unipolar depression. It also reviews the essential limitations of ECT – its adverse cognitive effects and high rates of relapse. The chapter introduces new developments in this field that have created forms of ECT administration that dramatically reduce the frequency and severity of adverse cognitive effects. These include critical alterations in the administration of ECT, such as the use of ultrabrief electrical stimuli, and the development of new forms of convulsive therapy, particularly Magnetic Seizure Therapy (MST) and Focal Electrically Administered Seizure Therapy (FEAST). Additional novel interventions such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) are also reviewed.

**Keywords:** electroconvulsive therapy (ECT), bipolar disorder, bipolar depression, unipolar depression, response rate, magnetic seizure therapy (MST), focal electrically administered seizure therapy (FEAST), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), vagus nerve stimulation (VNS)

Potential novel treatments for bipolar depression

**Summary**

Keming Gao, David E. Kemp and Joseph R. Calabrese

Pharmacological treatment of the maintenance phase of bipolar depression: Focus on relapse prevention studies and the impact of design on generalizability

The goal of pharmacological treatment of bipolar disorder is to prevent future occurrences of mood episodes. To achieve this goal, medications must demonstrate efficacy in the prevention of both manic/hypomanic and depressive relapses/recurrences. Currently, the efficacy of most pharmacological agents in the maintenance treatment of bipolar disorder has been studied using relapse prevention designs, in which only patients who tolerate and respond to a studied drug(s) in the acute phase (mania or depression) can enter the maintenance phase. Subsequently, the results from relapse prevention studies are not generalizable, not only because of the design, but also because of different index mood episodes. So far, however, only lithium and lamotrigine, and to some extent divalproex, have been investigated in both manic and depressive index episodes, while olanzapine and aripiprazole have been evaluated in manic index episodes. To facilitate the application of currently available data, this chapter will systematically examine randomized, blinded, controlled maintenance studies enrolling ≥ 100 patients and lasting ≥ 6 months.

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**Summary**

Harold A. Sackeim

Non-pharmacological somatic treatments for bipolar depression

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**Summary**

Carlos A. Zarate Jr and Husseini K. Manji

Potential novel treatments for bipolar depression
Existing pharmacological treatments for bipolar disorder (BPD), a severe recurrent mood disorder, is in general insufficient for many patients. Despite adequate doses and treatment duration, many individuals afflicted with this disease continue to experience mood episode relapses, residual symptoms, and functional impairment. In contrast to the manic phase of the illness where a fairly large variety of effective treatments are available, in bipolar depression effective therapeutics are scarce. This is especially troubling because the long-term course of BPD is dominated by recurrent depressive episodes and lingering depressive symptoms rather than hypomanic/manic episodes. Novel therapeutics – that is, drugs that do not include the existing antipsychotic, antiepileptic, and antidepressant medications – currently being studied to determine their efficacy and safety in bipolar depression include modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, memantine, ketamine, AMPA potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. Further study of these drugs will investigate their clinical utility in bipolar depression, and further our understanding of relevant drug targets.

Keywords: antidepressant, bipolar disorder, cholinergic, depression, dopamine, glutamate, melatonin, oxidative stress, treatment

Section D: Treatment of bipolar disorder in special populations

Summary

John L. Beyer and K. Ranga R. Krishnan

Late-onset bipolar disorder

Much is still unknown about late-life bipolar disorder (BPD), especially late-onset BPD. Late-onset BPD may be etiologically different from early-onset BPD, and may be related to the medical and neurological problems that can occur with aging; alternately, it may be an underlying progression of neurological illness associated with certain cases of BPD early in life.

Treatment of late-life BPD requires knowledge of ‘best treatment’ practices and an understanding of the effect aging has on psychopharmacotherapy. This chapter discusses the various treatment options available to this population. These include the mood stabilizers (e.g., lithium) and anticonvulsants (e.g., valproate, lamotrigine) most often used to treat BPD, as well as alternative treatments such as atypical antipsychotics and ECT. However, adequate clinical trials that would provide good evidence-based treatment recommendations for late-life BPD are not currently available. Therefore, extrapolation from trials in mixed-age populations and adaptation to the older patient is necessary to establish treatment recommendations.

Keywords: bipolar disorder (bpd), elderly, treatment, late-onset bipolar pharmacotherapy, comorbidity, epidemiology, lithium, valproate, antipsychotics

Summary

Robert L. Findling

Treatment of childhood-onset bipolar disorder

Because pediatric bipolar disorder is a serious condition, there is a substantive need for evidence-based treatments for children and adolescents suffering from this condition. A fundamental intervention used in this patient population is pharmacotherapy. Despite the importance of medication treatment in this patient population, only limited amounts of methodologically stringent data exist pertaining to this form of intervention. The evidence that
does exist suggests that some psychotropic medications can provide salutary effects for youths suffering from Bipolar I disorder. Also relevant is the pharmacotherapy of genetically at-risk children suffering from bipolar spectrum disorder, and treatment of psychiatric co-morbidities. Further placebo-controlled trials are needed in order to better characterize the efficacy and safety of psychotropic medication in this population.

**Keywords:** pediatric bipolar disorder, pharmacotherapy, acute treatment, maintenance therapy, lithium, atypical antipsychotics, mood stabilizers, anticonvulsants, children, adolescents

**Summary**

**Patricia Roy and Jennifer L. Payne**

**Treatment of bipolar disorder during and after pregnancy**

The treatment of bipolar disorder (BPD) in women is complicated by reproductive life events such as pregnancy and breastfeeding. This presents a clinical challenge to clinicians and patients who must balance risk of recurrent mood episodes against risks of potential teratogenic and adverse side effects of medications. It is important for the clinician and patient to develop an individualized plan of care during conception, pregnancy, delivery and postpartum to ensure maximum safety and minimal risks.

Pregnant women with BPD have the same risk of mood episodes as women who are not pregnant. There is clearly an increased risk for the development of mood episodes in the postpartum period – approximately 22–50% of women with BPD will develop postpartum depression (PPD). Risk factors for PPD in women with BPD include having a family history of PPD and depressive symptoms during pregnancy, but this risk can be significantly reduced with prophylactic medications. The risk for postpartum psychosis (PPP) is also significant, and most cases occur in the first 3 days following delivery. Risk factors include a history of an index manic episode, positive family history, and sleep deprivation during delivery.

Lithium is the first choice for mood stabilization during pregnancy for women with severe illness. The typical antipsychotics appear to be relatively safe during pregnancy. Venlafaxine, bupropion, mirtazepine, and the tricyclic antidepressants also all appear to be relatively safe in pregnancy. Patients should be monitored carefully during pregnancy. As the pregnancy progresses physiologic changes occur that alter the excretion of drugs and drug levels may change significantly, necessitating dose adjustments. In addition, factors such as vomiting due to morning sickness must be taken into account. Postpartum, women should be closely monitored, in labor and delivery, and at home. Medication changes made during pregnancy may have to be reversed as physiology reverses. If women choose to breastfeed, the pediatrician should be part of the clinical team.

**Keywords:** pregnancy, postpartum, breastfeeding, antidepressants, antipsychotics, mood stabilizers, benzodiazepines, postpartum depression, postpartum psychosis, neonatal

**Carlos A. Zarate Jr. and Husseini K. Manji**

**Conclusion**
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