

Conclusion

Carlos A. Zarate Jr and Husseini K. Manji

Laboratory of Molecular Pathophysiology & Experimental Therapeutics, Mood and Anxiety Disorders Research Program, National Institutes of Mental Health, National Institutes of Health, Bethesda, Maryland, USA

Although our knowledge of mood disorders in general is expanding steadily, comparatively little is known about bipolar depression in particular. The purpose of this book was to bring together clinicians and researchers, in order to offer the most up-to-date information about the diagnosis, treatment, and research surrounding bipolar depression.

Clinically, bipolar disorder continues to be one of the most debilitating medical illnesses. Afflicted patients generally still experience high rates of relapse, a chronic recurrent course, lingering residual symptoms, functional impairment, psychosocial disability, and diminished wellbeing. Furthermore, it is a sad fact that bipolar disorder is frequently unrecognized, misdiagnosed, and mismanaged. In Chapter 1, Dr. Marneros points out that depression and mania are mankind's oldest known mental disorders; they were the first mental disorders conceptualized by Hippocrates as a part of medicine, and mania and depression as two parts of the same disease was first described in the 1st century AD. Yet even today, a diagnosis of bipolar disorder is often missed in patients who report depressive rather than manic symptoms. Bipolar mania is often well-recognized by physicians, but bipolar depression, though more common, is often misdiagnosed and mistreated as unipolar depression. Thus, the depressed phase of bipolar disorder remains an enormous challenge for patients, their families, and clinicians. Furthermore, as Dr. Rihmer so poignantly discusses in Chapter 4, suicidal behavior in patients with bipolar disorder occurs almost exclusively during severe major depressive episodes and the suicide rate of untreated patients with bipolar disorder is 25 times higher than the same rate in the general population.

Undiagnosed patients with bipolar disorder often present for evaluation during a depressed episode. These patients are then most frequently misdiagnosed with unipolar depression and treated with antidepressants. For some patients, such treatment may be ineffective or deleterious for them. Much more research is needed to determine precisely which patients would benefit from short- and/or long-term antidepressant therapy. As Drs Young and Wang note in Chapter 6, there has long been debate about whether bipolar depression is similar to or different from unipolar depression, with the recognition that different

treatment responses and clinical courses suggest a different neurobiology. Drs Parker and Fletcher (Chapter 2) note that ‘bipolar depression’ is not a specific type of depression, with most episodes phenotypically weighted to melancholic or psychotic depression and that, clearly, the current diagnostic systems employ imprecise criteria to differentiate sub-types of bipolar disorder. Compounding this issue is that the lack of well-established guidelines for the diagnosis and treatment of bipolar disorder makes misdiagnosis even more likely.

As this volume discusses in some detail, mood stabilizing drugs are useful for treating different phases of bipolar disorder including the treatment of mania and depression acutely, and prophylaxis against relapse into either state. There is a general consensus that treating either acute depression or preventing relapses into depression is more challenging than treating mania, and that the drugs we use to treat the disorder are less effective for these symptoms. The thoughtful chapters by Drs Beyer and Krishnan, Findling, and Payne and Roy (13, 14, and 15, respectively), highlight the further difficulties associated with treating the disease in different populations.

Fittingly, the chapters in this volume highlight that the treatment of bipolar depression is another area where dramatic improvements are needed. In Chapter 9, Dr. Sachs points out that acute depression is the condition for which patients with bipolar disorder most often seek treatment; although the foundation of best clinical practice is double-blind, placebo-controlled trials with adequate sample size, in bipolar depression such evidence exists only for lamotrigine, quetiapine, olanzapine monotherapy, and olanzapine plus fluoxetine. 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. Furthermore, many depressed bipolar patients do not respond adequately to currently available treatments.

Expanding upon this idea, in Chapter 10 Drs Calabrese and Gao note that, so far, only lithium and lamotrigine, and to some extent divalproex, have been investigated in both manic and depressive index episodes. Dr. Sackeim (Chapter 11) gives a thorough overview of the usefulness of electroconvulsive therapy (ECT) in bipolar depression, as well as its essential limitations. His chapter introduces promising new developments in this field including new forms of ECT administration that dramatically reduce the frequency and severity of adverse cognitive effects, including alterations in the administration of ECT, Magnetic Seizure Therapy (MST) and Focal Electrically Administered Seizure Therapy (FEAST), as well as novel interventions such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). Similarly, Chapter 12 reviews some of the novel agents being explored to treat this population, focusing on drugs that do not include the existing antipsychotic, antiepileptic, and antidepressant medications. These include modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, ketaconazole, mifepristone, celecoxib,

mementine, creatine, and uridine RG2417. Although much of this work is preliminary, many of these agents have proven initially very promising, and further work will continue to explore their clinical utility in bipolar depression.

Despite these difficulties, the information contained in these chapters also highlights how far the field has progressed in recent years. In Chapter 6, Drs Wang and Young describe how many studies have shown altered neurobiology in patients suffering from bipolar disorder, including decreased brain volume and cell number in prefrontal and limbic regions, decreased serotonin metabolite 5-HIAA and serotonin transporter activity in cerebrospinal fluid, brain, or platelets of subjects with bipolar depression, decreased glucose metabolic rate and cerebral blood, and defects in mitochondrial electron transport chain and oxidative damage. In Chapter 8, Drs Savitz and Drevets give a thorough review of some of the pathophysiology of bipolar disorder, noting that reductions in gray matter volume and a concomitant increase in glutamatergic neurotransmission are 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 of patients with bipolar disorder. In Chapter 5, Drs Schulze and McMahon succinctly review the genetic evidence surrounding bipolar disorder and conclude that, although linkage and candidate gene association studies failed to deliver consistently replicable results, the advent of genome-wide association studies (GWAS) has spurred new hopes for the identification of true susceptibility genes. They note that after close to a century of genetic studies, bipolar disorder is emerging as a complex (non-Mendelian) disorder with a polygenic etiology.

Therefore, a better understanding of the genetics and molecular mechanisms of bipolar disorder, and particularly of bipolar depression, is critical to improving treatment for the disease. As the chapters in this volume attest, there is cause for hope. Research in recent decades has made great advances toward a better understanding of this illness so that better treatments can be developed. A better understanding of the neurobiological underpinnings of this condition, informed by preclinical and clinical research, will be essential for the future development of targeted therapies that are more effective, act more rapidly and are better tolerated than currently available treatments. Importantly, advancements in our understanding of the neurobiology of bipolar disorder continue to be made and do hold promise for future clinical applications.

Despite the devastating impact of bipolar depression on the lives of millions worldwide, there has been a dearth of knowledge concerning its underlying etiology and pathophysiology. This dearth, in turn, has undoubtedly contributed to the lack of development of improved therapeutic strategies for bipolar depression. Collectively, many questions remain unanswered regarding the diagnosis and treatment of patients with bipolar depression. To treat them more effectively, clinicians need additional diagnostic and screening tools, validated in a variety of practice settings; early detection and intervention programs; large-scale controlled clinical trials comparing the effectiveness of

novel interventions and single *versus* combination therapies; clinical studies to determine the most effective treatment regimens for patients with bipolar depression; and, finally, evidence-based standards for medications and psychosocial treatments. Much of that is lacking. However, as the information contained in this book has shown, new strides are being made daily in this field.