

Preface

Bipolar disorder (BPD) is a common, chronic, recurrent mental illness that affects the lives and functioning of millions of individuals worldwide, and is a major public health problem. Recent estimates suggest that BPD affects 1–2% of the general population (Goodwin and Jamison 2007). Indeed, the World Health Organization's (WHO) Global Burden of Disease noted that unipolar depression is the leading cause of disability worldwide, and that together mood disorders account over 10% of disability worldwide (World Health Organization 2008). A growing number of recent studies indicate that outcome is quite poor for many individuals with BPD. The illness is characterized by high rates of relapse, chronicity, lingering residual symptoms, subsyndromes, cognitive and functional impairment, psychosocial disability, and diminished well-being (Belmaker 2004).

Furthermore, available therapeutic options for the treatment of BPD are often insufficient for effectively managing the acute episodes, relapses, cyclicity, suicide attempts, and recurrences that are the hallmarks of this disorder, or for restoring premorbid functioning (Insel and Scolnick 2006; Machado-Vieira et al. 2008). Relatedly, a sizable proportion of patients with BPD fail to respond to or tolerate currently available treatments, especially for the treatment and maintenance of bipolar depression (Gitlin 2006; Judd et al. 2002). It is particularly sobering to note that, with the exception of lithium, all available Food and Drug Administration (FDA)-approved treatments for BPD are either anticonvulsant or antipsychotic drugs originally developed to treat other conditions (Zarate and Manji 2008). In our field, there is wide consensus that better treatments for BPD are urgently needed. "Better treatments" essentially means treatments that are more effective for more patients, that act faster, and that have fewer side effects. The inordinately high personal, familial, societal, and financial burden of this disorder underscores the urgent need to develop novel drugs to treat it.

BPD is, obviously, an extraordinarily complex disease. Previous neurobiological studies of mood disorders focused primarily on abnormalities of the monoaminergic neurotransmitter systems, on characterizing alterations of individual neurotransmitters in disease states, and on assessing response to mood stabilizer, antipsychotic, and antidepressant medications. The monoaminergic systems are

extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders (Drevets 2000). Studies of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding demonstrated a number of abnormalities in monoaminergic neurotransmitter and neuropeptide systems in mood disorders (Goodwin and Jamison 2007). Unfortunately, these observations did not greatly advance our understanding of the underlying biology of recurrent mood disorders, which must be able to explain the cyclic and often profound mood disturbances that can become progressive over time. BPD likely arises from the complex interaction of multiple susceptibility (and protective) genes and environmental factors, and the phenotypic expression of the disease includes not only mood disturbance but also a constellation of cognitive, drive, motor, autonomic, endocrine, and sleep/wake abnormalities.

However, the last decade has been a truly remarkable one for biomedical research. The “molecular medicine revolution” has brought to bear the power of sophisticated cellular and molecular biologic methodologies to tackle many of the society’s most devastating illnesses. While identifying the full human genetic sequence was a major step forward, many other advances of significant importance have aided our efforts to elucidate the pathophysiology of severe psychiatric illnesses. Indeed, psychiatry, like much of the rest of medicine, has entered a new and exciting age characterized by vastly improved technologies; these, in turn, have brought about both rapid advances in our knowledge and the promise of future gains in our understanding, particularly with regard to genetics, and molecular and cellular biology. For instance, the development of a multitude of new methodologies for brain imaging, genetic and genomic analyses, molecular engineering of mutant animals, novel routes for drug delivery, and sophisticated cross-species behavioral assessments makes it possible to study psychiatric and neurological diseases and disorders on the physiological level – from genes to cells, circuits, and illness phenotype. Thus, recent years have witnessed a more wide-ranging understanding of the neural circuits and the various mechanisms of synaptic and neural plasticity, the molecular mechanisms of receptor and postreceptor signaling, a finer understanding of the process by which genes code for specific functional proteins, and the identification of potential susceptibility and protective genes in many neuropsychiatric disorders, that, in toto, reduce the complexity in gene to behavior pathways.

Given the major public health problem posed by BPD, it should be obvious that we believe that a book highlighting the most recent research and clinical findings in BPD can bring much needed additional attention to this field. Our goal was to create the most informative and contemporary compendium of recent research into BPD. Toward that end, this volume assembles an impressive international array of major leaders from a broad swath of interrelated disciplines, from clinical phenomenology to basic molecular and cellular neurobiology, genetics, neuroimaging, and circadian physiology. The chapters contained herein provide a unique and broad perspective on BPD and the most recent research drawn from a variety of disciplines investigating this complex disorder.

The phrase “translational research” is one that has been used with increasing frequency in medicine in general, and neuroscience in particular. The National Institutes of Health (NIH) broadly defines translational research as “the process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease.” Translational research, which many of us are now engaged in, is the key to transforming scientific laboratory research into applications that benefit patient health and medical care and, in this context, the discovery of novel therapeutic agents. Translational research fuels our search to understand brain function, as well as the new ideas, new approaches, and new technologies used to ask and answer key questions about pathophysiology and disease mechanisms. Toward that end, the chapters collected in this volume clearly show how much has already been done to expand our knowledge of BPD.

In the opening chapter of the book, *Drs. Mitchell and colleagues* lay the foundation for this volume by exploring the course and outcome of this complex disorder. Their careful examination of clinical phenomenology is followed by several chapters describing the most recent genetic findings. As *Drs. McMahon and Wendland* so succinctly review, in the past few years significant progress has been made in finding common variants that might contribute to susceptibility for BPD. *Dr. Petronis and colleagues* note that epigenetic research has great potential to enhance our understanding of the molecular basis of BPD, and their chapter reviews the epidemiological, clinical, and molecular findings in BPD from the perspective of inherited and acquired epigenetic misregulation. Next, *Drs. Glahn and Burdick* introduce the concept of endophenotypes – indicators of processes mediating between genotype and phenotype – and present data suggesting that neurocognitive and personality traits appear to be appropriate endophenotypes for BPD.

Two chapters exploring the use of animal models discuss the way that such models are being used to refine and expand our knowledge of BPD; *Dr. Einat* describes endophenotype- and lesion-based models in BPD, and *Dr. Chen* discusses genetic-based animal models. Both chapters highlight how the use of animal models has the potential to greatly accelerate the research process and spawn new hypotheses and discoveries in all areas of biomedical research. Notably, these two chapters also discuss the challenges of creating a truly physiologically representative animal model to study BPD. These thoughtful and comprehensive chapters underscore the point that while no perfect animal model exists for any aspect of any CNS disorder, the limitations and strengths of most models have been extensively empirically investigated, and these issues are particularly important now, given the rapid growth of genomic and proteomic technologies.

These chapters are followed by a number of chapters offering a thorough and unique overview of the neurobiology of BPD. The chapter by *Dr. Walderhaug and colleagues* opens this portion of the book with a comprehensive review of the neurotransmitters serotonin, norepinephrine, dopamine, and acetylcholine, and the role these systems play in BPD. *Dr. Benes* then describes the variety of abnormalities affecting the gamma aminobutyric acid (GABA)ergic system that have been identified in postmortem studies of the corticolimbic system. *Drs. Gawryluk and Young* provide a valuable and comprehensive overview of the signal transduction

pathways involved in the molecular biology of BPD and the indications for the mechanisms of disease and treatment. These concepts are expanded in the chapter by *Dr. Du and colleagues* exploring the role of synaptic and neural plasticity in the pathophysiology of BPD. Finally, *Dr. Kato* provides a fascinating overview of the evidence for mitochondrial dysfunction in BPD.

Taken together, these chapters highlight how our evolving knowledge of neuroplasticity is revolutionizing our understanding of disease etiology in BPD. In this regard, BPD is treated first as a disease with molecular underpinnings that is susceptible to environmental and genetic regulation. These molecular underpinnings point to targets for the development of novel pharmacotherapeutics. Cellular signaling cascades regulate the multiple neurotransmitter and neuropeptide systems implicated in CNS disorders and are targets for the most effective treatments. The next level of integration is through brain circuitry, particularly how molecular events and adaptations to genetic or environmental vulnerabilities result in maladaptive communication within and between regions of the brain that regulate behavior.

Two chapters give a thorough overview of the most recent neuroimaging findings in BPD. *Drs. Savitz and Drevets* highlight findings suggesting that BPD is being increasingly recognized as a neuropathological disorder characterized by reductions in grey matter (GM) volume, and neuronal and postmortem glial cell changes. *Drs. Blumberg and Blond* review converging functional neuroimaging evidence implicating state and trait dysfunction in a ventral prefrontal cortex–amygdala neural system in BPD. These chapters highlight how neuroimaging continues to be a tremendously useful tool in BPD research; indeed, translational imaging has been particularly valuable in the neurosciences where, due to the inaccessibility of the human brain, the use of radioisotopes (PET and SPECT) and MRI is central to the assessment of brain penetration, target engagement, brain function, and neuropathology. In addition, the chapter on sleep and biological rhythm abnormalities in the pathophysiology of BPD by *Drs. Levenson and Frank* carefully reviews the known sleep and biological rhythm abnormalities associated with BPD; the chapter describes the nature of these circadian rhythm abnormalities and reviews the evidence supporting their role in bipolar episodes.

The closing chapters of this book are devoted to exploring treatment strategies for BPD, including both traditional and novel therapeutics, as well as non-pharmacological treatments. In his chapter, *Dr. Bowden* describes the practical issues of selecting and adapting medications to treat the specific clinical features of a patient with BPD – with an emphasis on specific guidelines – and emphasizes the tactics needed to accomplish this specific to individual medications. *Dr. Loo and colleagues* review the non-pharmacotherapeutic, somatic treatments that play an essential role in the management of BPD, most notably electroconvulsive therapy (ECT). Finally, our closing chapter on potential novel therapeutics for BPD reviews a number of key targets/compounds that could result in putative novel treatments for BPD. As these chapters highlight, both currently available and novel therapeutics for this disorder offer significant treatment advantages over those available just 5 or 10 years ago.

As mentioned above, the broad concept of translational research is key to our progress, because it gives us the tools to integrate disparate findings and make sense of them. Translational research essentially helps us to create a bridge between basic science and clinical developments and between clinical development and practice. It is our hope that the thorough and comprehensive overview of recent research provided in these pages will provide readers with a way to make sense of the many novel findings presented, to extract integrated themes, and to draw insight from the diverse chapters.

Acknowledgments

We would like to acknowledge the support of the Intramural Research Program of the National Institute of Mental Health (I.D.H., C.A.Z.), the Stanley Medical Research Institute (C.A.Z.), and NARSAD (C.A.Z.).

USA

Carlos A. Zarate Jr
Ioline D. Henter
Husseini K. Manji

References

- Belmaker RH (2004) Bipolar disorder. *N Engl J Med* 351:476–486
- Drevets WC (2000) Neuroimaging studies of mood disorders. *Biol Psychiatry* 48:813–829
- Gitlin M (2006) Treatment-resistant bipolar disorder. *Mol Psychiatry* 11:227–240
- Goodwin FK, Jamison KR (2007) Manic-depressive illness: bipolar disorders and recurrent depression, 2nd edn. Oxford University Press, Oxford
- Insel TR, Scolnick EM (2006) Cure therapeutics and strategic prevention: raising the bar for mental health research. *Mol Psychiatry* 11:11–17
- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59:530–537
- Machado-Vieira R, Salvadore G, Luckenbaugh DA, Manji HK, Zarate CA Jr (2008) Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. *J Clin Psychiatry* 69:946–958
- World Health Organization (2008) The global burden of disease: 2004 update. World Health Organization, Geneva
- Zarate CA Jr, Manji HK (2008) Bipolar disorder: candidate drug targets. *Mt Sinai J Med* 75:226–247

Behavioral Neurobiology of Bipolar Disorder and its
Treatment

Manji, H.K.; Zarate Jr., C.A. (Eds.)

2011, XVI, 347 p., Hardcover

ISBN: 978-3-642-15756-1