Potential novel treatments for bipolar depression

Carlos A. Zarate Jr and Husseini K. Manji

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

Abstract

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.

Introduction

Previous chapters of this volume explored the epidemiology, definition, classification, outcome, and currently used pharmacological treatments for bipolar depression. However, it is becoming increasingly clear that current pharmacotherapies are insufficient for many patients with bipolar depression. For instance, a large-scale study funded by the National Institute of Mental Health (NIMH) failed to find any benefit to antidepressant use for patients with Bipolar I and II depression over the course of 26 weeks [1]. In contrast to the manic phase of the illness, where a fairly large variety of effective treatments are available – most notably antipsychotic and antiepileptic agents – in bipolar depression efficacious therapeutics are scarce. This is especially worrisome because the long-term course of bipolar disorder (BPD) is dominated by recurrent depressive episodes and lingering depressive symptoms rather than hypomanic/manic episodes [2].

This chapter will review the efficacy and safety of several novel therapies for bipolar depression. Promising drug targets and agents for bipolar depression involve several systems, including the melatonin and serotonergic
(5-HT2C receptor) systems, the dopaminergic system, the glutamatergic system, and the hypothalamic-pituitary adrenal (HPA) axis. In addition, the GSK intracellular signaling cascade, the arachidonic acid cascade, and the oxidative stress system appear to be worthy of further study. This chapter will review several specific agents, including modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, memantine, ketamine, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. Table 1 summarizes the use and profile of these drugs, all of which meet the category of clinical evidence rating (see Ch. 9) of B, C, or D. The chapter does not review studies in which the treatment of bipolar depression was not the primary issue. Omega-3 fatty acids will also not be reviewed here as they have been extensively reviewed elsewhere (see [3]) and because a large, randomized, controlled study failed to find significant benefits for their use in bipolar depression [4]. Finally, we will not review non-pharmacological somatic treatments (see Ch. 11 for a thorough review of this topic).

**Drugs that affect multiple systems**

**Modafinil**

Modafinil is currently approved by the U.S. Food and Drug Administration (FDA) as a wakefulness-promoting agent for the treatment of excessive daytime sleepiness in narcoleptic patients [5]. The presumptive mode of action of this drug is currently unknown, but is hypothesized to be multisystemic in origin. Modafinil has been reported to affect the following neurotransmitter systems: glutamate, GABA, hypocretin, and to a lesser extent, the dopaminergic and noradrenergic systems [6].

Clinically, modafinil appears to benefit patients with mood disorders, particularly in cases where sedation is clinically troublesome. In a 6-week, randomized, double-blind, placebo-controlled evaluation of modafinil (mean daily dose 177 mg) in subjects with bipolar I or II depression who did not adequately respond to mood stabilization with or without adjunctive antidepressant therapy (n = 87), there was both greater baseline to endpoint change and change in week 2 onwards in patients treated with modafinil than with placebo [7]. No manic switches were reported. In another study, Frye and colleagues (unpublished, reported in [8]) compared the add-on modafinil (100 or 200 mg in the morning for 3 weeks) to placebo in the treatment of patients with BPD who also had residual fatigue, depressive symptoms, or both. The study drug was significantly more effective than placebo on a variety of scales, including baseline to endpoint change on the Inventory for Depressive Symptoms (IDS), percentage response rate, remission rate, and Clinical Global Impression (CGI) improvement. In addition, modafinil was not found to be significantly associated with treatment-emergent mania. One published