available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Review

Bipolar pathophysiology and development of improved treatments

*Charles L. Bowden**

Department of Psychiatry, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Mail Code 7792, San Antonio, Texas 78229-3900, USA

ARTICLE INFO

Article history:
Accepted 27 May 2008
Available online 11 June 2008

Keywords:
Bipolar
Mood disorder
Drug treatment
Genetics
Endophenotypes
Diagnosis

ABSTRACT

The purpose of this review is to provide strategies and their rationale which can facilitate scientifically productive investigations into genetic, neuronal, brain functional and clinical aspects of bipolar disorder. The presentation addresses both factors that have impeded and those that have facilitated landmark advances on the pathophysiology and treatment of bipolar disorders. Application of the strategies can provide a scientific platform that may be useful to basic and clinical scientists for the purposes of achieving seminal advances in understanding pathophysiology, including inherited and experience based contributors to disease expression. Current diagnostic criteria omit certain key symptoms, do not include illness course or family history and lack specification of the importance of fundamental symptomatology. Consideration of such factors in inclusion and exclusion criteria, and in assessment instruments in basic and clinical studies, serves to strengthen the capability of a research plan to test key hypotheses regarding moderating and mediating factors of this complex illness. For example, most studies of brain structure and function and of new interventions have selected subjects on the basis of traditional full syndromal criteria. Evidence indicates that additional consideration of principal behavioral domains of bipolar symptomatology, e.g., anxiety, psychosis, impulsivity, elevated psychomotor and cognitive processing speed, rather than strictly depressive or manic syndromes can provide more homogeneous samples for study, and increase the focus of experimental hypotheses.

Contents

* Fax: +1 210 567 3759.
E-mail address: bowdenc@uthscsa.edu.

0006-8993/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2008.05.084

1. Introduction

Bipolar disorder, recognized by Hippocrates and Areteus, has received renewed scientific interest consequent to development of effective, novel treatments over the past 50 years. Certain features of bipolar disorder and its scientific study have facilitated these landmark developments, while others have impeded advances. This review focuses on both the facets of bipolar disorder which have aided advances and several methodological approaches which have impeded or slowed advances. A principal aim of the review is to suggest those research strategies which hold the best promise for providing a scientific platform that will aid basic and clinical scientists in achieving seminal advances in understanding pathophysiology, including inherited and experience based contributors to disease expression in bipolar disorders. Experience based factors contributory to bipolar disorders are better understood than genetic factors. These include hypothalamic pituitary axis dysregulation, early life psychological and physiological insults, e.g., CNS infections, use of abusable drugs, and vascular or traumatic brain injury. The limited advances to date from genetic studies are in part consequent to the flawed syndromal phenotype currently in vogue. DSM criteria largely resolve problems of criterion variance, but both include false positive cases and exclude true positive ones.

2. Diagnostic criteria

Current diagnostic criteria for bipolar disorders, whether in the Diagnostic and Statistical Manual-IV-TR, (DSM-IV-TR) or the International Classification of Diseases-10, have both strengths and limitations (American Psychiatric Association, 2000). The strengths come from an aim of the Research Diagnostic Criteria, which provided the conceptual basis for all subsequent versions of the DSM, to reduce criterion variance across clinicians assessing the same clinical information. Thus, a mental health professional seeing a patient in any country with the same set of symptoms will arrive at the same or nearly same diagnosis, including secondary identification of severity. The criteria for mania are quite specific and selective. Therefore, enrollment of subjects while acutely manic into studies is likely to yield a highly representative sample, with little likelihood of enrollment of false positive cases.

The limitations deal with temporal requirements, lack of specification of core symptoms, failure to incorporate several behavioral characteristics which are highly characteristic of bipolar disorders, and no utilization of family history or illness course data. Two temporal problems exist. The duration of symptoms required for an episode is a minimum of 7 days for mania, 4 for hypomania, or hospitalization for the acute illness state. Hospitalization is less frequently employed as a management technique in the 21st century than it was a quarter century ago, both because of the quicker effectiveness of the array of antimanic agents currently available than was the case with lithium when it was the only recognized antimanic agent and more emphasis on ambulatory than hospitalized based care. However, particularly for early onset bipolar in adolescence and prepubertal youth, hypomanic symptoms are often present for 1 or 2 days and in some instances even shorter periods (Angst, 1998; Geller et al., 2001; Angst et al., 2003). Further complicating this is the evidence that mixed states, rather than strictly depressed or manic/hypomanic syndromes, constitute the majority of syndromal level cases in adolescents (Craney and Geller, 2003; Dilsaver et al., 2005).

The second temporal issue is that only cross sectional, current symptoms are specifically utilized in supporting a syndromal diagnosis. This does not allow consideration that the proportion of time symptomatic, both syndromally and subsyndromally, is much higher in bipolar than major depression (Goldberg and Harrow, 2004) and that persons with bipolar I disorders may have had a manic syndrome briefly many years ago, but experience only subsyndromal manic symptoms in the present, thus not be diagnosable as bipolar (Akiskal, 1996; Judd et al., 2002; Kupka et al., 2007).

Non-psychiatric disorders often have core symptoms or signs that must be present to establish a diagnosis, but which do not require presence of secondary or less consistent illness features to make the diagnosis. In contrast, bipolar requires that at least one of three classical manic symptoms; elevated, expansive or irritable mood be present, despite evidence that the first two symptoms are less prevalent than are, for example, core behavioral disturbances of increased activation motorically and cognitively (Wicki and Angst, 1991; Bowden et al., 2006). Alternatively, irritability can substitute for these, but, in such instances, an additional symptom is required to confirm diagnosis. The second level symptoms listed in DSM-IV-TR have two problems. Most allow more than one symptom to suffice. For example, agitation or psychomotor slowing can qualify, despite their lack of equivalence. Additionally, several symptoms highly characteristic of bipolar clinical states are not recognized. These include reduced sexual drive in bipolar depression and, in manic states, increased sexuality, risky behavior, impulsivity, increased evening energy, and affective lability. This last group is particularly useful in recognizing illness features that are indicative of bipolarity even when individuals are not syndromally ill, and have been incorporated into screening scales for bipolar disorder (Angst et al., 2005). Bipolars have higher rates of positive family histories for bipolar but also for any mood disorder, bipolar or unipolar (Geller et al., 2001; Hirschfeld and Vornik, 2004). In addition, bipolar has its onset before age 20 in at least half of individuals, a considerably earlier onset than observed for major depression (Kupfer et al., 2002), (Hirschfeld et al., 2003).

A consequence of these distorting criteria for diagnosis is that many studies will under recognize bipolarity, and thereby run a risk of including in control groups persons with bipolar features (Hantouche et al., 1998). This in turn often leads to intervention for depression with use of antidepressants without attention both psychoeducationally and with mood stabilizers to the fundamental bipolarity, and, consequently, a poor course of illness (Ghaemi et al., 2000). Authorities have proposed both short term and long term strategies for overcoming and/or minimizing the undesirable consequences of present schema. Several of these can be implemented without changes in DSM-IV TR criteria. The task force working toward