CHAPTER

1

The Scope of Bipolar Disorders

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1.1 DIAGNOSTIC AND PUBLIC HEALTH ASPECTS

Recent advances in the epidemiology, psychopathology, and pharmacotherapy of bipolar disorders have led to a greater recognition of this illness in all of its varieties (Akiskal *et al*., 2000; Maj *et al*., 2002; Goodwin and Jamison, 2007). The lifetime risk for bipolar conditions is about 1% for the core (bipolar I) phenotype, making it at least equal in prevalence to schizophrenia. A higher percentage of acute psychiatric hospital admissions is now being assigned to the category of mania, and recognition of clinically attenuated outpatient forms of the illness (soft bipolar spectrum) is increasing. The latter (Bipolar II and beyond) is now estimated to be at least three to four times more prevalent than bipolar I (Angst *et al*., 2003; Judd and Akiskal, 2003; Hirschfeld *et al*., 2003); the current US prevalence of bipolar spectrum disorders, including bipolar I, is estimated at 4–5% (Merikangas *et al*., 2007).

Reasons for the current focus on the entire diagnosable range of bipolar conditions are several. Predominant among these is the tendency of diagnostic practice to follow the availability of effective treatment modalities (Lehmann, 1969). After the discovery of chlorpromazine, North American psychiatrists were tacitly encouraged to elicit subtle degrees of formal thought disorder from their patients so as to bring them the benefits of this new class of drugs. By the early 1970s, schizophrenia had become more or less synonymous with psychosis. With the advent of lithium carbonate treatment and its well-documented efficacy for bipolar disorders, this trend became reversed in favor of bipolar disorders. Beginning with DSM-III (American Psychiatric Association, 1980), the concept of schizophrenia has been largely restricted to a core group of deteriorating psychotic disorders, while mood disorders have been broadened to include even those with mood-incongruent psychotic features that may or may not coincide with affective episodes. This diagnostic approach reflects more than just therapeutic fashion; it is supported by familial aggregation, course, and outcome (Akiskal, 2002). Available evidence indicates that mood disorders are often recurrent and, especially in bipolar conditions, can lead to considerable impairment in developmental, conjugal, and social spheres. The public health significance of bipolar disorder is summarized in Table 1.1. The most important of these is suicide, seen in as many as 20% of those who receive inadequate or no

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Table 1.1 Public health aspects of bipolar disorder.

Lifelong cyclical illness
1.0–1.5% of population
Peak onset 15–30 years
5–10 year delay in correct diagnosis
Frequent hospitalization
Repeated hospitalization
Repeated conjugal disruption: promiscuity
Repeated job change/loss
Financial disasters
Alcohol/substance abuse
50% nonadherence to medication
Increased cardiovascular mortality
Suicide (highest within 10 years of illness onset)

treatment, and must be considered a *preventable* complication (Khuri and Akiskal, 1983; Akiskal, 2007). It now appears that bipolar II may account for a disproportionately large portion of suicidal morbidity and mortality among bipolar disorders (Rihmer *et al*., 1990; Rihmer and Pestality, 1999; Akiskal, 2007), emphasizing the importance of early and accurate diagnosis.

At the "softest" end of the spectrum, milder degrees of bipolar disorder – subsumed under the rubrics of cyclothymic disorder (Akiskal *et al*., 1977) and bipolar disorder not otherwise specified – are now categorized as mood disorders rather than being grouped with neurotic or personality disorders. Although these seemingly attenuated and "atypical" variants may not be easily distinguishable from nonaffective personality disorders, the clinician is advised to err on the side of affective diagnosis because of treatment implications, including their potential to engage in suicidal acts (Azorin *et al*., 2010).

External validating strategies – such as family history, course, and inter-episodic temperamental features – are often necessary to confirm the diagnosis of the bipolar spectrum (Akiskal, 2003). The most established of bipolarity beyond classic mania and bipolar I (Akiskal, 1999) is the bipolar II type, so-named originally by Dunner, Gershon, and Goodwin (1976). Like diabetes type II, its onset is often insidious, but its ravages no less devastating than that of the psychotic forms of the illness. This is particularly true for cyclothymic depression, a variant of bipolar II we have termed bipolar II$^1/_2$ (Akiskal *et al*., 2006), arising from a cyclothymic temperament, it pursues an unstable course; and is likely to be misdiagnosed as axis II cluster B (Akiskal, 2004). These patients represent the "dark side" of bipolarity (Akiskal, Hantouche, and Lancrenon, 2003; Hantouche, Angst, and Akiskal, 2003).

The American Psychiatric Association Diagnostic Manual of Mental Disorders, even in its last published edition (DSM-IV, 2000), does not recognize hypomanic or manic switches occurring during pharmacotherapy, electroconvulsive therapy, phototherapy, and sleep deprivation as indicators of bipolar disorder. These patients are obviously not unipolar MDD, nor are they classified under bipolar NOS. Therefore, this common clinical phenomenon is voted by the DSM Committee out of existence. Since at least 1983, there

has been good evidence that such switching of antidepressants requires bipolar family history (Akiskal *et al*., 2000; Akiskal, Hantouche, and Lancrenon, 2003). They are best regarded as less penetrant forms of bipolar disorder (bipolar III). Diagnostic studies of depressive states with mood swings in the setting of multiple drug abuse, particularly that of stimulants, is controversial, but we contend that many of these individuals belong to a provisional bipolar type III-½ (Akiskal and Pinto, 1999; Maremmani *et al*., 2003; Camacho and Akiskal, 2005). This is relevant in a book on advances in bipolar disorder, because many of these patients respond favorably to anticonvulsant mood stabilizers. Finally, I would like to mention bipolar type IV, which refers to individuals who develop depression later in life from a lifelong background of hyperthymic temperament (hypomanic traits without clear cut episodes); their bipolar status might be inferred from familial bipolarity (Cassano *et al*., 1992). It is uncertain how DSM-V in progress will deliberate on the status of bipolar spectrum disorders. Suffice it to say that their public health significance (that is,, early diagnosis and treatment) warrants a more appropriate nosological designation than the inglorious dumping ground of "bipolar NOS."

In a French national study (see Table 1.2), 65% of all major depressions belonged to the bipolar spectrum, of which the most prevalent were the bipolar II and II½ phenotypes (Akiskal *et al*., 2005b, 2006). These considerations are important, because nearly all pharmacologic treatments covered in this book – certainly those approved by regulatory bodies – pertain to bipolar I. Thus, there is a wide gap between the psychopharmacology of bipolar disorder and the public health significance of the phenotypes observed in the community and the clinic.

Lithium was the first specific agent for bipolar disorder for clinical use. This was four decades ago. Many other agents have been approved since then, almost all of them in the last decade. They are all covered in this book. Lithium medicalized psychiatry in bringing significant attention to the course of bipolar disorder. Its importance should not be overshadowed by these new developments. Many patients, especially those in the "core" classic form of the illness (mania-depression free interval type, (Koukopoulos *et al*., 1995; Goodwin and Jamison, 2007)), do respond to lithium. Its judicious use, often in combination with other agents in rational polypharmacy, requires intimate knowledge of its physiological and medical characteristics. Regrettably, young psychiatrists are not

Table 1.2 Bipolar spectrum subtypes in the French EPIDEP study (n = 493): validation by bipolar family history.

	N	%
Bipolar I	41	8.4
Bipolar II	61	12.4
Bipolar II-½	164	33.5
Bipolar III	28	5.7
Bipolar IV	22	4.5
Total	319	64.5

Akiskal *et al*., *J Affect Disord*, 2005b.

having adequate experience with this agent. A summary of the medical workup of patients in preparation of lithium use (see Akiskal, 1999) is given in Appendix 1.A.

1.2 PSYCHOLOGICAL AND SOCIAL ASPECTS

The long term, essentially life-long, nature of bipolar disorder, and its vicissitudes dictate continuity of treatment and long-term caring. To solve practical problems in the patients' lives requires caring that goes beyond medications and psychotherapy, to include the family, significant others, and the community.

Bipolar disorder continues to be poorly understood by both the public and doctors. More often than not, a bipolar child is classified as having conduct disorder or ADHD (Dilsaver, Henderson-Fuller, and Akiskal, 2003). A teenager's suicide attempt is misattributed to problems of the heart, adolescent crisis, or substance abuse; promiscuous behavior is blamed on early "sexual abuse." Bipolar patients from time to time describe their parents as "monsters" or "emotionally-abusive," which some psychotherapists accept on blind faith without ever talking to the parents or significant others. Bipolar II patients are often diagnosed as unipolar and/or borderline personality (Akiskal, 2004), treated with antidepressant without mood stabilizers, resulting in tragic aggravation of the course of the illness (Akiskal and Mallya, 1987; Akiskal *et al*., 2005a). Excessive spending or squandering of one's economic resources and pathological generosity may lead to financial ruin before bipolarity is considered.

Polls of members of the Depressive and Manic-Depressive Association in the U.S. have shown a latency of 10 years from the onset of symptoms until the correct diagnosis of bipolar disorder (Hirschfeld, Lewis, and Vornik, 2003). Early diagnosis is critical, because suicide in bipolar patients often occurs within this early period. The comfort, support, destigmatization, information, and advocacy provided by such a conglomeration of patients, families, and community leaders (many of whom are themselves bipolar) represents a novel approach in the rehabilitation of the bipolar patient into society. This is a humane and just cause.

Given that a proportion of bipolar individuals have artistic and leadership talents (Akiskal and Akiskal, 1988), sophisticated clinical management of bipolarity can potentially safeguard the adaptive capacity and contributions that gifted bipolar people provide to society. Although psychotically ill (bipolar) patients are represented in the media as being creative, this is a destigmatization campaign at best and glamorizing madness at worst. Achievement and creativity are attributes of the "softer" spectrum represented in the attenuated temperamental expressions of bipolarity often involving and extending into bipolar II (Akiskal and Akiskal, 1988, 2005).

To what extent cognitive dysfunction in bipolar illness precedes clinical onset is not entirely settled. Nor is it known how it specifically impacts functioning and creativity. These are new vistas of scientific investigation (Torres *et al*., 2010; Frangou, 2009; Germana *et al*., 2010; Giakoumaki *et al*., 2010). Goodwin and Jamison (2007), based on animal studies, raise the possibility that early treatment with certain agents used in bipolar disorder might increase neuronal growth and thereby contribute to better cognitive functions. This is an open field of investigation for the next generation of

neuroscientists and psychopharmacologists in this area (Burdick *et al*., 2007; Goldberg and Chengappa, 2009).

Spanning from temperament to psychosis, bipolar disorder is a fascinating yet tragic human condition. Mental health professionals who treat these individuals must use pharmacotherapy and psychosocial interventions compassionately, judiciously, and rigorously, – only rarely "aggressively." Severe bipolar illness is not just an ordinary illness to be medicated to "mediocrity." The temperament of these individuals deserves all our consideration and respect. While most *psychotic* bipolar patients are neither leaders nor creators, they are the reservoir of the genes, which in dilute form, might be the seeds of genius (Akiskal *et al*., 2000).

APPENDIX 1.A: LABORATORY CONSIDERATIONS IN THE CLINICAL USE OF LITHIUM

More than any other development, the introduction of lithium has emphasized the role of physicianship in psychiatry. The scientific literature and clinical wisdom on the therapeutic aspects of this salt have been well summarized in a monograph by Jefferson *et al*. (1983). The success of lithium treatment is dependent on the thoroughness of the initial workup, on dosage titration procedures, and on appropriate monitoring throughout therapy.

The type of workup depends on the age of the patient and concurrent medical conditions (Table 1.3). In young (less than 40 years), physically healthy subjects, preparation for lithium therapy should include medical history (especially focused on neurologic, renal, cardiac, gastrointestinal, endocrine, and cutaneous systems), physical examination, and laboratory evaluation focusing on electrolytes and thyroid. In older patients or those with a history of cardiac disease, a baseline electrocardiogram (EKG) should be obtained and an electroencephalogram (EEG) performed if brain disease is suspected; if there is a history of renal disease, thorough evaluation of baseline kidney function is mandatory. Given rigorous indications for lithium, major medical illness, and abnormalities in laboratory indices do not necessarily contraindicate its use; they do dictate, however, greater medical vigilance, including frequent determination of blood levels and use of lower doses.

Table 1.3 Recommended laboratory workup of patients considered for lithium therapy.

Healthy <40 years	All others
Weight	EKG
CBC	EEG
T4/TSH	TRH test
FBS/serum electrolytes	24-h urine volume
Urinalysis	Urine concentration test
BUN/creatinine	Creatinine clearance

A short-term lithium trial in the controlled environment of a hospital is relatively easy to administer and is recommended for acutely manic, medically ill, or elderly subjects. In outpatient practice, the physician must make sure that the patient and significant others understand the importance of adherence to periodic laboratory procedures and monitoring of side effects.

Lithium is rapidly and completely absorbed from the gastrointestinal tract and peaks in the serum in about 1.5–2.0 (standard preparation) or 4.0–4.5 hours (slow release preparation), depending on age. Its half-life varies from 24 to 36 hours; steady state is reached in about four days. Lithium is not protein-bound and is excreted unchanged almost entirely through the kidneys. It can be safely combined with most classes of drugs except diuretics and nonsteroidal anti-inflammatory agents (other than aspirin), which tend to increase the serum lithium level.

Acutely manic- and possibly bipolar depressive-patients have a high tolerance for lithium and preferentially retain it during the first 10 days while excreting sodium; a regular diet is recommended. Postpubertal bipolar patients, who typically have excellent glomerular function, require higher doses to achieve the same level of equilibrium in the serum. The reverse is true in the geriatric age group. Elderly subjects with adequate glomerular function can benefit considerably from judicious lithium use. However, greater medical vigilance is required for this group; initial doses should be low (150–300 mg/day), with frequent clinical and laboratory monitoring to maintain blood levels in the lower range (0.3–0.8 mEq/l). Special attention must be paid to signs of sinus node dysfunction (bradycardia) or neurotoxicity; the latter is particularly likely in patients with concurrent neurologic disease or sedative and alcohol abuse.

In healthy subjects who achieve good episode prevention, quarterly serum levels (12 hours after the last dose) and serum creatinine are generally sufficient; thyroid indices must be obtained at least once a year. For elderly or medically compromised patients, laboratory tests should be repeated as dictated by the medical condition, with frequent serum lithium levels; the dosage should be kept at the lowest possible level compatible with prophylaxis.

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