The search for the wandering thymostat: a review of some developments in bipolar disorder research

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This brief review of some of the recent issues in research into bipolar disorder will serve as an introduction to the rest of this supplement, which comprises the proceedings of the First European Stanley Foundation Symposium on Bipolar Disorder, held at the Royal Society, London, 24 and 25 September 1998.

BIPOLAR DISORDER

Bipolar disorder was recognised many hundreds of years ago, forgotten, and then rediscovered in the 20th century. The longitudinal course of recurrent affective illness was recognised as important, and the term 'bipolar disorder' was first introduced to differentiate a recurrent, cyclical mood disorder in which people experience episodes of elated mood as well as depression. It became clear that the bipolar–unipolar separation did not differentiate all cyclical or recurrent mood disorders in which shifts in polarity occur and further subtypes were described to encompass other clinical manifestations as follows: bipolar I disorder, bipolar II disorder, bipolar III disorder, false unipolar disorder, and sub-syndromal bipolar disorders (cyclothymia, hyperthymia and dysthymia). The background to the development of these classifications and their historical context have been reviewed by Goodwin & Jamison (1990) and Akiskal (1996).

Bipolar I disorder

Bipolar I disorder is the classic manic–depressive psychosis in which episodes of mania and depression occur, usually at well-spaced intervals.

Bipolar II disorder

Bipolar II disorder was introduced as a subtype of bipolar disorder to include the group of patients who experience recurrent depressive and hypomanic, but not manic, episodes (Dunner *et al*, 1970; Angst, 1978). As a diagnostic category, bipolar II disorder appears robust, with a typically stable symptom profile, differences in outcome from bipolar I disorder and a tendency to 'breed true' (Gershon *et al*, 1982; Coryell *et al*, 1984, 1987, 1989, 1995; Endicott *et al*, 1985; Dunner, 1993). Differences have been found between bipolar I and II disorders on magnetic resonance imaging (MRI) scanning and on the presence of vascular abnormalities, including Raynaud's phenomenon, migraine and 'migraine equivalents' (Endicott, 1984; Altshuler *et al*, 1995). Lithium discontinuation studies have also demonstrated differences between the two conditions (Faedda *et al*, 1993). The defining factor for bipolar II disorder is the presence of hypomania but not mania, and difficulties in definition of hypomanic symptoms may have led to heterogeneity in assessed samples (Winokur *et al*, 1993; Coryell, 1996). These problems have been partially resolved with the introduction of DSM–IV (American Psychiatric Association, 1994) criteria for bipolar II disorder, although the exclusion of antidepressant-induced hypomania and the duration of hypomanic symptoms needed to reach diagnostic criteria for an episode have been questioned (Akiskal, 1996).

Bipolar III disorder

Bipolar III disorder (pseudo-unipolar bipolar disorder) refers to a more heterogeneous grouping of people who experience recurrent episodes of unipolar depression and also show clinical features suggesting that they may go on to develop a hypomanic or manic episode. Such people may have a family history of bipolar disorder, exhibit antidepressant-induced hypomanic switching, or have hyperthymic, dysthymic or cyclothymic premorbid temperaments (Cassano *et al*, 1988; Akiskal, 1996).

False unipolar disorder

The term 'false unipolar' is applied to recurrent depressions originally classified as unipolar, but with the subsequent development of mania or hypomania requiring reclassification as bipolar. The proportion of 'false unipolars' in the diagnosis of unipolar depressive disorder has been estimated at between 10.7% and 28.4% (Goodwin & Jamison, 1990).

Sub-syndromal bipolar disorders

Hyperthymia, dysthymia and cyclothymia have been described as long-term components of personality – persistent temperamental dysregulations – which may later give rise to episodes of mood disorder (Kukopulos *et al*, 1983; Akiskal, 1996; Akiskal & Cassono, 1997). Cyclothymia is characterised by switches between two poles of mood and behaviour: one phenomenologically similar to bipolar depression, atypical depression and dysthymia, with hypersomnia, hyperphagia, lethargy and tearfulness; and the other characterised by decreased sleep, increased energy and jocularity. Hyperthymia resembles the 'upper' of these poles, perhaps with occasional spells of dysthymia, while dysthymia resembles the 'lower' pole and may be accompanied by a major depressive episode (double depression), or hypomania following a major depressive episode (Keller *et al*, 1983; Klein *et al*, 1988).

Epidemiology

The life-time prevalence rates of both bipolar I and bipolar II disorders have been estimated at 0.6%, giving a combined figure of 1.2% (Weissman & Myers, 1978). The combined prevalence of bipolar II, bipolar III and dysthymic disorders has been estimated at 7.8–12% (Depue *et al*, 1981).

Cycle frequency

Cycle frequency of mood variation in bipolar disorder varies in a range from illness-free spells of many years' duration, with apparent peaks at multiples of 1 year, to mood variations of an extreme form occurring over the course of hours or minutes (Goodwin & Jamison, 1990). A sub-classification has been developed, determined by the cycle frequency of mood variation within the course of the condition: rapid cycling, ultrarapid cycling, ultra-ultrarapid (ultradian) cycling, mixed states and continuous cycling. 'Normal cycling' has not been defined. Rapid cycling has been defined as the occurrence of four or more episodes of significant mood disturbance in a year.

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Ultrarapid cycling involves cycle frequencies in the range of weeks to days, and ultradian cycling involves significant mood variation within a day (Bauer *et al*, 1994). Mixed states may be seen either as coexisting depressive and (hypo)manic symptoms or as an extreme of rapid cycling. Continuous cycling refers to the absence of illness-free spells between episodes (Goodwin & Jamison, 1990).

Antidepressants and psychoactive substance misuse have been implicated in the development of rapid cycling, which appears to be a complication predominantly of bipolar II disorder (Wehr & Goodwin, 1979; Kukopulos *et al*, 1980; Bauer *et al*, 1994). Other organic factors, including seizure threshold abnormalities and thyroid dysfunction, may relate to the development of accelerated mood cycles. Rapid cycling is associated with a high risk of suicide (Fawcett *et al*, 1987). The origins and treatment of rapid cycling have recently been reviewed (Ahmed & Morriss, 1997). Mixed affective states, in which depressive and (hypo)manic symptoms either alternate so rapidly that they may become indistinguishable, or coexist, are increasingly recognised. The DSM–IV classification includes non-induced mixed states with bipolar I disorder. Rapid cycling, commonly induced by pharmacological agents in bipolar II disorder, may be confused with mixed states and lead to misclassification. Mixed states have implications for treatment, with even a modest degree of depressive symptomatology present during a manic episode indicating a greater chance of response to an anticonvulsant agent than to lithium (Calabrese & Delucchi, 1990; Swann *et al*, 1997).

Relationship between subtypes

Although bipolar I and II disorders appeared to be diagnostically stable over a 10-year follow-up period (Coryell *et al*, 1995), with only 5% of bipolar II 'converting' to bipolar I, there is more interaction between the 'soft bipolar' conditions, which include bipolar II and III, and the temperamental variants, cyclothymia, hyperthymia and dysthymia. Few (6%) people with cyclothymia switch to bipolar I disorder, but 25% switch to bipolar II (Akiskal *et al*, 1977).

Prospective follow-up of patients with apparently unipolar depression demonstrated a 20% switching rate into bipolarity, although some of this high figure may be the result of ascertainment bias. The clearest markers for this switching are the presence of antidepressant-induced hypomanic episodes, onset in young adulthood, hypersomnia, retardation, family history and post-partum episodes (Strober & Carlson, 1982; Akiskal *et al*, 1983).

Another study of the rate of conversion from apparent unipolarity to bipolarity revealed rates of 8.6% conversion to bipolar II and 3.9% to bipolar I. Patients converting to bipolar II disorder had a more protracted course of illness and demonstrated temperamental instability, with mood lability the most specific (86%) although least sensitive (42%) predictor of switching (Akiskal *et al*, 1995).

Sub-syndromal bipolarity appears to become apparent at a mean age of 14 years, while the initial episode of bipolar I disorder occurs at a median age of 18 years and bipolar II disorder at a median age of 21 years (Depue *et al*, 1981; Goodwin & Jamison, 1990).

Comorbidity

An important, potentially confounding variable is the high rate of comorbid substance misuse in bipolar disorder, as high as 50% in cyclothymia and 46% in bipolar I disorder in the Epidemiologic Catchment Area study (Goodwin & Jamison, 1990). Women with bipolar II disorder are more likely to drink alcohol to excess (12%) than those with bipolar I disorder (0%). Men with bipolar I and II disorders have equal likelihoods of problems with alcohol, at rates of 19% and 20% respectively (Dunner *et al*, 1979; Hensel *et al*, 1979). People with bipolar disorder may have a particular sensitivity to mood-altering agents. It has been suggested that the high rate of substance misuse represents either attempted self-medication or a character trait that may predispose people to developing bipolar disorder (Goodwin & Jamison, 1990; Winokur *et al*, 1994; Akiskal, 1996).

Birth season effects

People with bipolar disorder appear to show an excess of spring and winter births. This finding appears consistent and may suggest a causal mechanism (Moore *et al*, 1996; Torrey *et al*, 1996), or may be the result of parental bipolarity leading to increased activity the preceding summer.

Organic and neuropsychological issues

The view that patients with bipolar disorder make a full recovery between episodes of illness has been widely accepted despite a lack of systematic investigation. Neuropsychological impairment has been identified in depression and mania (Wolfe *et al*, 1987; Sackheim & Steif, 1988) but has always been thought to be entirely a state effect. Imaging studies have shown the presence of patchy white matter lesions (PWMLs) in the brains of patients with bipolar disorder, particularly those with poor outcome (Videbech, 1997). Such lesions may be associated with neuropsychological impairment (particularly of executive function) in healthy elderly subjects and in patients with unipolar depression or bipolar disorder (DeCarli *et al*, 1995; Dupont *et al*, 1995; Lesser *et al*, 1996). It has been suggested that cognitive deficits in bipolar disorder may persist after clinical recovery (Trichard *et al*, 1995) or in states of remission (Coffman *et al*, 1990; Morice, 1990). Direct evidence of impairment, particularly in frontal executive function, has been found in euthymic bipolar I disorder (van Gorp *et al*, 1998; Ferrier *et al*, 1999). Furthermore, there is evidence that such impairment may precede the onset of illness (Gourovitch *et al*, 1999; Sigurdsson *et al*, 1999) and may be worsened by illness progression (Kessing, 1998; van Gorp *et al*, 1998).

Evidence has accumulated that some patients with bipolar disorder have structural changes in the brain such as smaller temporal lobes or caudate nuclei on MRI (Elkis *et al*, 1995; Videbech, 1997). Not all patients show these abnormalities, which tend to be more frequent with increasing age, although they may be found in younger patients. The pathological basis of these abnormalities and of the PWMLs found in excess in bipolar disorder (Altshuler *et al*, 1995; Videbech, 1997) is unknown. Measurements of brain metabolism by positron emission tomography (PET) show a hypofrontal pattern of metabolic activity in bipolar disorder which persists despite improvements in the patient's clinical state (Martinot *et al*, 1990). A study by Drevets *et al* (1997) showed reduced blood flow in the subgenual area deep in the prefrontal cortex in both bipolar and unipolar depression. The decrease in blood flow appeared to be partly accounted for by a reduction in cortical volume, which was observed in both symptomatic patients and those in remission.

CONCLUSION

The concept of bipolar disorder has expanded from one in which there are major

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pathological variations in mood of a severe, extreme form, to one in which more subtle variations are found, which merge imperceptibly with 'normal' mood variation. These milder forms appear to be common. They may become more severe under some circumstances and show some degree of progression. The triggers for such progression can be socially, pharmacologically or hormonally mediated. A complex interaction between genetic predisposition, personality, 'stress' and life events, modified by processes such as behavioural sensitisation, the glucocorticoid cascade, limbic kindling and the actions of pharmacological agents, and substance misuse, appears to mediate such changes in severity (Post *et al*, 1986; Goodwin & Jamison, 1990; O'Brien, 1997). These functional changes are accompanied in some cases by structural changes of unknown pathological origin and uncertain significance, which are associated with neuropsychological deficits. Although the structural and neuropsychological changes worsen with age and/or illness progression, there is evidence suggesting that such changes may precede illness onset or are present early in the condition. These observations suggest that organic factors have a part to play in the causation of this disorder, perhaps through subtle neurodevelopmental changes or by direct damage, and may also be related to the course and outcome in these (and perhaps all) patients. Carefully conducted longitudinal studies of cohorts of patients and those at risk are required to tease apart the contribution of various aetiological factors – research that could have profound implications for the choice and timing of treatments.

The articles in this supplement expand on the issues raised above. First, there is a section on the neurobiology of depression. Dr Manji and colleagues from Wayne State University, Michigan, describe insights into bipolar disorder originating from neurobiological research that has been stimulated by observations on the efficacy of lithium and anticonvulsants. A review of the neuropsychology of bipolar disorder from Dr Murphy (University of Cambridge) and Dr Sahakian (MRC Cognition and Brain Sciences Unit, Cambridge) follows. The molecular pathology of bipolar disorder is reviewed in contributions from Professor Craddock and Dr Jones (University of Birmingham) and from Professor Blackwood and colleagues (University of Edinburgh). Dr Sun from the Stanley Neurovirology Laboratory at Johns Hopkins University, Baltimore, Maryland, and colleagues outline some of the issues related to gene expression in bipolar disorder. Dr Baumann and Dr Bogerts from the University of Magdeburg describe neuroanatomical studies in these and related conditions.

These contributions are followed by a review of old and new treatments for bipolar disorder. Dr Cookson from the University of London considers the current status of lithium, while Dr Calabrese and colleagues from Case Western Reserve University, Cleveland, Ohio, discuss the theoretical and practical aspects of bipolar maintenance research. Professor Scott of the University of Glasgow describes emerging research in cognitive behaviour therapy for bipolar disorder. The treatments described above are efficacious in bipolar disorder but there are great problems in achieving clinical effectiveness in the field. Dr Post (National Institute of Mental Health, Washington, DC) and colleagues describe the Stanley Foundation Bipolar Network. The development of better treatment options in bipolar disorder is discussed by Dr Kupka (University Medical Centre, Utrecht) and colleagues. Dr Tondo (University of Cagliari, Sardinia) and colleagues outline research on the clinical effectiveness of lithium. Finally, Dr Geddes and Professor Goodwin from the Psychiatry Department of the University of Oxford review the evidence base for effective treatments in bipolar disorder and describe a way forward for future trials which test not only efficacy but also effectiveness.

These contributions describe the current state of development in some areas of bipolar research in the late 1990s. It is proposed that the Stanley Foundation sponsor a symposium in Europe on bipolar research every 2 years, to alternate with the international meeting on bipolar research held biennially in Pittsburgh.

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