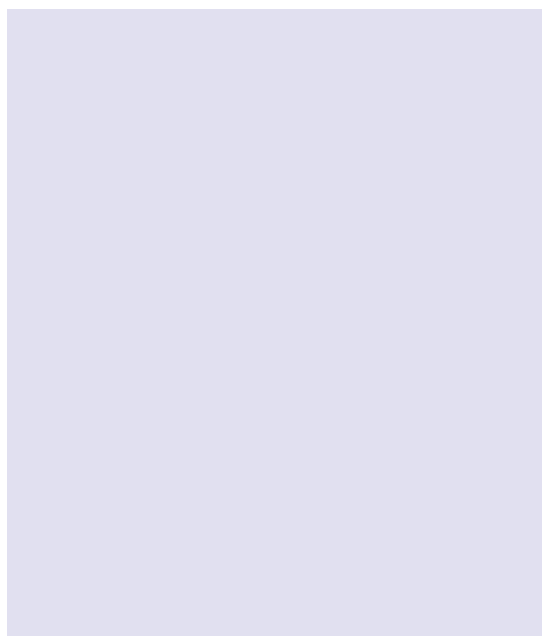


BIPOLAR DISORDER

— aetiology and pathophysiology

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Bipolar disorder is characterised by recurrent manic or hypomanic and depressive episodes. The first part of this month's special feature describes the clinical features, epidemiology, aetiology, diagnosis and pathophysiology of the disorder



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Galen was among the ancient Greeks who made key observations about mood disorders

Mood disorders have been recognised since ancient times. Hippocrates (460-357BC) attributed melancholia (ie, depression) to an excess of “black bile” and mania to an excess of “yellow bile” and Galen (131-201AD) wrote that melancholia manifested in “fear and depression, discontent with life, [and] hatred of all people”. Aretaeus of Cappadocia (in about 150AD) observed that melancholia and mania could be linked together in the same illness and said of disease sufferers: “They are prone to change their mind readily; to become base, mean-spirited, illiberal, and in a little time . . . extravagant, munificent, not from any virtue of the soul, but from the changeableness of

the disease.” Although our understanding of bipolar disorder and the means to treat the condition have moved on since these times, the observations of the ancient Greeks (eg, that depression and mania have a biological basis and are associated with recognisable symptoms) remain relevant today.

SYMPTOMS AND FEATURES

Bipolar disorder is characterised by recurrent episodes of mania or hypomania (a mild to moderate level of mania) and depressive episodes with patients reverting to an outwardly normal (ie, euthymic) state in between. The condition can result in harmful effects on psychological, physical occupational and social wellbeing.

Current practice subdivides the illness into two main forms: bipolar I disorder and bipolar II disorder. In bipolar I disorder, mania predominates — the disease being characterised by the occurrence of one or more manic (or mixed, ie, a patient shows signs of depression and mania at the same time) episodes, usually with the occurrence of one or more major depressive episodes. In bipolar II disorder, mania is milder and depression predominates — the disease being characterised by the occurrence of one

or more major depressive episodes accompanied by at least one hypomanic episode.

Variations include rapid-cycling disorder, where patients have four or more episodes of illness within a year. Where a patient has depressive episodes but no manic (or hypomanic) episodes, they are said to have unipolar (ie, clinical) depression, which was the subject of a *Hospital Pharmacist* special feature in 2002.¹

Somatic symptoms are also reported by patients. These generally relate to a disturbance of hypothalamic function, affecting sleep and appetite, and to other endocrine changes, such as to adrenal and thyroid glands. Severe episodes of mania or depression can include symptoms of psychosis.

EPIDEMIOLOGY

Approximately 1 per cent of the population will develop bipolar disorder throughout their lifetime,² with bipolar I disorder generally being more predominant.

Rates of bipolar I disorder appear to be consistent across different cultures and ethnic groups³ and both sexes are affected equally. Bipolar I disorder is ranked within the top 30 World Health Organization defined causes of disability world-wide.⁴

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Panel 1: Symptoms of mania or hypomania used to diagnose bipolar disorder using a categorical approach

A diagnosis of mania or hypomania can be made from the concurrent presence of at least three of the following symptoms:

- Grandiosity or inflated self-esteem
- Decrease in the need for sleep
- Talkativeness (pressured speech)
- Flight of ideas (rapidly racing thoughts and flitting of ideas)
- Marked distractibility
- Increased goal-directed activity/psychomotor agitation
- Excessive involvement in pleasurable activities without regard for negative consequences (examples are unrestrained buying sprees, sexual indiscretions, foolish business ventures)

Symptoms must be severe enough to impair function markedly or require hospital admission to prevent harm to self or others. The possibility of symptoms being caused by schizophrenia, schizoaffective disorder or substance abuse must be excluded.

Depression due to any cause (including bipolar II disorder) is ranked within the top five WHO defined causes of disability world-wide.

— DIAGNOSIS

Well before the current (fourth) edition of the American Psychiatric Association's, "Diagnostic and statistical manual of mental disorders" was published in 2000, there was an emphasis on using a "categorical system" to diagnose bipolar disorder. Under a categorical system, diagnosis is based on determining the presence (or absence) of a number of carefully described clinical features, without a great deal of consideration being given to issues such as aetiology.⁵ (This approach was based on the work of Emil Kraepelin, an eminent late 19th/early 20th century German psychia-

trist who was also responsible for recognising the differences between schizophrenia and bipolar disorder.) Examples of the features used to diagnose the mania/hypomania components and the depressive components of bipolar disorder using the categorical approach are set out, respectively, in Panels 1 and 2.⁵

The clearer criteria for diagnosis that using a categorical approach brings has aided research into bipolar disorder. For example, it has become possible to develop standardised assessment tools that have encouraged bigger, multi-centre studies into clinical aspects of the illness and assessment of the efficacy of treatments.

Further improvements in diagnostic accuracy will require better understanding of the neurobiological substrates of the affective disorders and how these relate to clinical manifestations.

Panel 2: Symptoms of depression used to diagnose bipolar disorder using a categorical approach

A diagnosis of depression can be made where five or more of the following symptoms have been present during the same two-week period and represent a change from previous functioning:

- Depressed mood
- Markedly diminished interest or pleasure in all or most activities
- Significant weight loss when not dieting, or weight gain, or a decrease or increase in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive inappropriate guilt
- Diminished ability to think or concentrate or indecisiveness
- Recurrent thoughts of death or suicidal thoughts, or a suicide attempt

Symptoms must be severe enough to cause significant distress or impairment in social, occupational or other important areas of functioning. The possibility of symptoms being caused by substance abuse or being the immediate result of a bereavement must be excluded.

— AETIOLOGICAL FACTORS

Genetic factors Evidence from epidemiological and twin studies strongly suggests that bipolar disorder is an inheritable illness. First-degree relatives of patients with bipolar disorder have significantly higher rates of mood disorder than do relatives of non-affected comparison groups. For example, concordance rates (ie, rate of co-occurrence of the disease in both twins) for bipolar I disorder are greater than 50 per cent in monozygotic twins compared with around 20 per cent for dizygotic twins.⁶

While various models of inheritance have been proposed, the genetic factors involved remain elusive, although many potential gene candidates have been identified. Modern molecular biological techniques now permit the screening of multiple gene candidates and suggest strongly that multiple, rather than few, genes are involved in the varying clinical presentations of bipolar populations. Bipolar illness is now best viewed as complex genetic illness with several important susceptibility genes interacting with a variety of environmental contributions to increase the risk of a person developing the disorder.

Life events, environmental stress and personality Most clinicians have long believed that a relationship exists between stressful life events and the incidence of depressive relapse in bipolar illness. For example, research supports the hypothesis that major losses, including death, divorce, health and financial crises, can be associated with depressive episodes. Studies have also linked the development of depression with parental loss in early life through death or separation.⁷ Clearly such disruptions are not in themselves sufficient to cause depression as less than 20 per cent of the population who experience losses develop depression.

Why some people who have suffered loss relapse into depression is not known. Psychoanalytic thinking suggests that the anger experienced towards the real or imagined loss of the loved object is hypothetically turned inwards on the self. This hypothesis, while attempting to explain the loss of self-esteem found in depression, does not explain the expression of hostility in some patients experiencing depression. Another theory, the cognitive behavioural model of depression proposes that depressed mood (particularly hopelessness and helplessness) results from negative expectations and beliefs.⁸ Cognitive psychotherapy aims to alter these negative cognitive processes. Research in these areas is difficult to do well, and (with the exception of cognitive behaviour therapy, which has had good results in some patients with bipolar disorder) psychodynamic ideas are generally more of theoretical value in helping psychiatrists formulate and understand an individual's case.

There is also believed to be a link between stress and mania, although this is less well studied than that between stress and depression. One reason for this is that the heightened self esteem of patients experiencing a manic episode can make them less receptive to requests to study their condition.

— PATHOPHYSIOLOGY

The pathophysiology of bipolar disorder as a whole is still relatively poorly understood. What is known (from animal models, neuroimaging, electrophysiological, neurotransmitter and second messenger system studies) is that it is a highly complex illness involving a profound alteration in brain and somatic systems.

Certain aspects of the illness, in particular the biological basis of depression, have been studied extensively over a number of years. A failure of regulation of the neurotransmitter noradrenaline (NA) is currently implicated in depression/depressive episodes. Initial evidence from the 1950s and 1960s (eg, that the NA-depleters reserpine and tetrabenazine caused depression) suggested that a simple depletion of NA at critical sites was involved.⁹⁻¹¹ More recent evidence, however, has reported that normal or elevated levels of NA activity are evident in depression, suggesting that the situation is more complicated.¹²

Serotonin (5-HT) is also implicated in depression. For example, decreased concentrations of 5-HT metabolites are found in the cerebrospinal fluid of suicide victims and there is evidence that remissions induced by antidepressant treatment can be reversed by depleting precursors of plasma tryptophan (itself a 5-HT precursor).

Less work has been done to establish the underlying cause of mania. It has been suggested that it is a hyperdopaminergic state (and hence the effect of antipsychotic drugs that block dopamine transmission in treating manic episodes - see p135-7). A depletion of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA) is also advocated as an underlying cause - hence stimulating GABA (for example, using valproate) has a role in managing mania.

Similarly, little is known about the underlying disturbances that cause patients to cycle between mania, euthymia and depression. Studies carried out in the 1960s and 1970s suggested that a neuronal electrolyte imbalance was responsible for mania (and that lithium, as a small cation of a similar size to sodium, might prevent manic relapse by replacing sodium at key sites), but these theories have now fallen somewhat out of favour. Lithium is also known to inhibit the recycling of inositol phosphates, key components of some cellular systems, but the exact

role of this effect in preventing manic relapse is not understood.

Neuroanatomical studies on post-mortem brains have shown that patients with either bipolar disorder or unipolar depression show subtle structural deficits in the dorsal raphe but that patients with bipolar disorder have more neurones in the locus caeruleus than unipolar depressed patients.¹³ The clinical significance of these findings is not yet known.

— CONCLUSION

Bipolar disorder is a complex illness with several factors likely to play a role in its development. Given the nature of the symptoms involved (ie, somatic as well as those relating to the central nervous system) it is little wonder that affected individuals find it impossible to follow the advice of well meaning friends, or even physicians, to "pull themselves together and get on with it".

Unfortunately, despite decades of investigation, we still have few studies that are helpful in clinical, as opposed to research, settings. We do, however, have an increasingly diverse set of pharmacotherapies, including antidepressants, targeting different neurotransmitter systems, mood stabilisers and atypical antipsychotics that are helping to revolutionise our approach to the treatment of the bipolar disorders.

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