Major advances in bipolar disorder

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ABSTRACT

- There have been major advances in clinical understanding and treatment of bipolar disorder over the past decade.
- Randomised controlled trials of pharmacological treatments and psychological interventions have shown that there are effective short-term and long-term treatments for the disorder.
- Despite advances in treatment, diagnosis is often delayed or mistaken, and many people who could benefit are not using the treatments available.
- Functional and symptomatic recovery from episodes of bipolar disorder is frequently less complete than previously considered, and disability is often profound.
- Although manic episodes are the distinguishing feature of bipolar disorder, it appears that depression is the predominant mood disturbance and that much of the functional impairment associated with bipolar disorder results from this. Comorbidity with anxiety disorders or substance misuse is common.
- Advances in genetics, brain imaging and basic pharmacology are starting to provide understanding of the complex causative processes.

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In recent years, there has been a heightened and long-overdue public and professional awareness of bipolar disorder (manic–depressive illness). While lay appreciation of depression and schizophrenia has improved dramatically over the past decade, understanding of bipolar disorder has lagged. However, public figures such as Olympic swimmer John Konrads,[1] astronaut Buzz Aldrin and actress Carrie Fisher (of "Star Wars" fame) have recently spoken out about their struggles with this condition. Media interest has been enhanced by reports such as a recent Access Economics / SANE Australia document, which estimated the cost burden of bipolar disorder in Australia to be $1.6 billion a year.[2]

The increased community interest in bipolar disorder parallels significant advances in the scientific understanding and treatment of the condition, which will be the focus of this article.

Diagnosis

Bipolar disorder is usually subdivided into bipolar I and bipolar II disorders (Box), although it is debatable whether these represent truly distinct forms of the condition or merely differences in severity.

Although bipolar disorder is usually considered a distinctive condition, the diagnosis is often delayed or missed. A recent survey by the US National Depressive and Manic–Depressive Association[3] found that, although a third of patients sought help within 1 year of illness onset, another third waited at least 10 years before seeking help. Sixty-nine per cent reported being misdiagnosed before being given the appropriate diagnosis, having consulted an average of four medical practitioners in the process. The most common misdiagnosis was unipolar depression (60%), followed by anxiety disorder (26%), schizophrenia (18%), borderline or antisocial personality disorder (17%), alcohol or substance misuse or dependence (16%) and schizoaffective disorder (11%) (some patients reported more than one misdiagnosis).

Epidemiology and comorbidity

Recent Australian data from the National Survey of Mental Health and Well-being[4] indicate that one in 200 Australians have active features of bipolar disorder in any 12-month period. Prevalence figures differ, however, depending on how illness severity is defined. For example, using a broad definition of bipolar II disorder (ie, incorporating shorter periods of hypomania), bipolar disorder prevalence rates of up to 11% have been reported.[5]

Comorbidity with other psychiatric illnesses is common, particularly with anxiety disorders and substance misuse. For example, in the Australian national survey,[4] 52% of people with bipolar disorder had a concurrent anxiety disorder (most commonly panic disorder, generalised anxiety disorder or social phobia) and 39% a substance-use disorder. In fact, drug misuse was even more common in people with bipolar disorder than in those with unipolar depression. There is a complex interrelationship between bipolar disorder and drug misuse — drugs are often used to self-medicate against emotional and psychotic symptoms, but, conversely, some drugs (particularly marijuana) are potent inducers of manic destabilisation. While some authorities have proposed that such comorbid conditions may reflect the essential biology of the illness, it would appear more likely that such conditions reflect a secondary "psychological scarring" resulting from the traumas of dealing with the condition.

Bipolar depression and suicide

Although hypomania and mania are the distinguishing diagnostic characteristics of bipolar disorder, it is becoming increasingly apparent that the depressed phase of this condition (bipolar depression) is the predominant mood[6] and that it is clinically distinct from unipolar depression.[7] Two recent studies from the large US longitudinal Collaborative Depression Study have highlighted this. After following patients over an average of 13 years, Judd et al[8,9] reported that those with bipolar I or bipolar II disorder spent much more of their lives depressed than manic or hypomanic. Those with bipolar I disorder experienced 32% of the weeks of follow-up in depression, compared with 9% of their time

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Bipolar disorder terminology

Bipolar I disorder

At least one lifetime episode of mania, and usually (but not necessarily) episodes of depression. May also include episodes of hypomania.

Bipolar II disorder

Episodes of both hypomania and depression. No manic episodes.

Mania

Episodes of pathologically elevated (and/or irritable) mood of at least a week in duration; associated characteristic symptoms and behavioural changes indicative of disinhibition, poor judgement, grandiosity and increased speed of thoughts, speech and behaviour; marked functional impairment, psychotic features or hospitalisation.

Hypomania

Episodes of pathologically elevated (and/or irritable) mood of at least several days in duration; associated characteristic symptoms and behavioural change indicative of disinhibition, poor judgement, grandiosity and increased speed of thoughts, speech and behaviour; distinctly different from the individual's normal functioning; no marked functional impairment, psychotic features or hospitalisation.

Mixed episodes

Episodes characterised by the concurrent presence of manic/hypomanic and depressed features (usually the manic/hypomanic features predominate). Sometimes referred to as "dysphoric mania".

Rapid-cycling bipolar disorder

Four or more episodes of mania, hypomania, depression or mixed episodes within a 12-month period.

in mania or hypomania — a ratio of 3 : 1. For those with bipolar II disorder, the disparity was even greater, with 50% of the time consumed by depression, compared with 1% spent in hypomania. Furthermore, for patients with either bipolar I or bipolar II disorder, the less severe forms of depression (minor, dysthymic or subsyndromal) predominated over major depression in time. Yet, as discussed below, even such lesser severities of depression can cause great disability.

Suicide rates in people with bipolar disorder remain unacceptably high, at between 10% and 19% — 15 times that of the general population.[10] At least a quarter will attempt suicide, a rate even higher than that seen in unipolar depression.[4] The depressed phase of bipolar disorder is linked to about 80% of suicide attempts and completed suicides.[11] Mortality rates from natural causes (mainly vascular disease) are also increased in people with bipolar disorder.[12]

Disability and impaired function

It appears that the disability associated with bipolar disorder has been historically underestimated. In the Australian national survey, people with bipolar disorder were almost five times more likely than the general population to have disrupted relationships, and more than twice as likely as those with unipolar depression to have such difficulties.[4] Disability — as measured by the number of days on which the individual could not perform his or her major role — was even more marked than in people with unipolar depression. Most studies have reported higher unemployment rates and a greater likelihood of being on government benefits than the general population. A US study[13] reported that people with bipolar I disorder were 15 times more likely to be in the lowest income-earning category.

It is becoming increasingly apparent that the depressed phase of bipolar disorder is a significant contributor to the disability associated with this condition. Bauer et al[14] reported that the functional impairment in a sample of war veteran outpatients correlated significantly with their depressive, but not manic, symptoms. In a healthcare utilisation study of a large US private insurer, Bryant-Comstock et al[15] found that people with bipolar disorder incurred three to four times the healthcare costs of the average patient treated in the organisation, with bipolar depression incurring the highest expense. Furthermore, the disability appears not to be related merely to the presence of *major* depression. Altshuler et al,[16] examining a sample of patients with bipolar I disorder who had subsyndromal depressive symptoms, reported that there was still a correlation between functional level and the severity of the depression — the greater the severity of depression, the lower the functional level.

Neurobiology

The biological underpinnings of bipolar disorder are slowly being revealed. A strong genetic contribution to causation has been confirmed by both a large twin study, which estimated a heritability rate of about 85%,[17] and a Danish population sample of several million, which reported a 13-fold increased risk in first-degree relatives.[18] Despite much research, the responsible genes involved have proved elusive, with a large international meta-analysis unable to confirm chromosomal regions of genome-wide significance.[19] However, the demonstration of regions associated with schizophrenia in an accompanying study provides promise that specific genes will ultimately be verified for bipolar disorder.[20]

There has been a resurgence of interest in the pharmacological action of lithium,[21] with particular interest in its effect on the phosphoinositide system and the enzyme glycogen synthase kinase-3, both components of intracellular signal transduction pathways. Neuroimaging studies of brain structure have yielded only tentative findings. However, functional imaging using techniques such as proton spectroscopy and functional magnetic resonance imaging hold great promise — demonstrating, for example, regional metabolite changes[22] and differential patterns of activation in the various phases of the illness.[23,24]

Treatment

There have been substantial advances in treatment since the last review of bipolar disorder in the Journal in 1991.[25] The first Australian national clinical practice guidelines on the treatment of bipolar disorder have recently been published.[26] As controlled trials have only been undertaken in patients with bipolar I disorder, guidance on the management of bipolar II disorder has been extrapolated from that, although it is uncertain whether this is appropriate.

However, despite improvements in treatment, health service utilisation rates by people with bipolar disorder remain low. For example, in the Australian national survey[4] only a third of people with current symptoms of mental illness were in contact with a mental health professional, and 40% were not taking medication for their condition.

Short-term treatment of mania and mixed episodes

An increasing number of new agents have been demonstrated in randomised controlled trials (RCTs) to be effective for managing acute episodes of mania. (In the following text, National Health and Medical Research Council levels of evidence[27] are indicated in brackets.) The anticonvulsants carbamazepine and valproate have been found to be effective for treating mania (E1). So, too, have a number of the atypical antipsychotics (olanzapine [E1] and risperidone, aripiprazole and quetiapine [all E2]), which were initially developed for schizophrenia. Recent Cochrane database meta-analyses (E1) have confirmed the efficacy of valproate[28] and olanzapine.[29] These reports suggested that olanzapine may be more effective than valproate, although the former is more likely to produce weight gain.

Although it is now more than 50 years since John Cade's seminal report on the efficacy of lithium for treating acute mania was published in the Journal,[30] the value of this medication continues to be substantiated in contemporary studies (E1). It is still regarded by regulatory authorities, such as the US Food and Drug Administration and the Australian Therapeutic Goods Administration, as the "benchmark" comparator agent for trials of potential new antimanic agents. A meta-analysis by Poolsup et al[31] has confirmed the efficacy of lithium for treatment of acute mania.

There have been few controlled studies of patients with mixed episodes. The best evidence for efficacy in treating mixed episodes is for valproate (E2), which has been shown to be more effective than lithium or placebo.[32]

Short-term treatment of bipolar depression

Until a few years ago, there had been a dearth of controlled trials on bipolar depression, and those undertaken involved only small samples. Traditionally, the major treatments for bipolar depression have been antidepressants (E2) (or occasionally lithium [E2]), with the major disadvantage being the propensity for antidepressants to induce either manic episodes or a rapid-cycling pattern of illness.

In 1999, Calabrese et al[33] reported that the anticonvulsant lamotrigine, taken alone, was more effective than placebo. Subsequent studies (discussed below) have shown that lamotrigine also prevents recurrence of bipolar depression (E2).[34,35] Lamotrigine does not appear to be effective in treating unipolar depression.[36] The limiting clinical features of lamotrigine are the development of rash (Stevens–Johnson syndrome may occur) and the related necessity for slow-dose titration.

The other new agent of interest for treating bipolar depression is olanzapine, particularly in combination with the selective serotonin reuptake inhibitor fluoxetine (E2). Recently, Tohen et al[37] reported that olanzapine was more effective than placebo for treating bipolar I depression (E2), although the benefit was not profound. The more dramatic finding of their study was the high response rate (56%) among those receiving the combination treatment compared with those receiving olanzapine only (39%) or placebo (30%). Although this is just one study whose findings clearly require replication, it is nonetheless of significant import.

Long-term treatment of bipolar disorder

Pharmacological treatments

Three agents (lithium [E1], lamotrigine [E2] and olanzapine [E2]) have now been confirmed to be effective for maintenance treatment.

The greatest weight of evidence is for lithium, with a Cochrane meta-analysis confirming its prophylactic activity.[38] It is also worth noting that the prophylactic benefit of lithium has been confirmed by its efficacy when employed as an active comparator in the lamotrigine and olanzapine trials. In fact, its benefit may have been underestimated in those trials, as its overall efficacy was clear, irrespective of the fact that some participants were probably lithium non-responders. Lithium has also been reported to reduce suicide rates independently of its prophylactic capacity.[39] The mechanism of this action is unknown. There has also been much interest in the potential clinical ramifications of laboratory studies indicating that lithium has neuroprotective properties.[40]

Perhaps the most novel finding in the prevention of bipolar disorder relapse has arisen from two 18-month RCTs comparing lamotrigine, lithium and placebo in patients with bipolar I disorder.[34,35] Both studies found lamotrigine to be more effective than placebo in preventing depressive relapse, with a limited efficacy against mania that was only demonstrable in analyses of pooled data from both studies.[36] In these trials, lithium was, conversely, more effective than placebo in preventing manic relapse and less effective against depression (again, only apparent in the pooled data). These findings suggest that the combination of lithium and lamotrigine may be particularly advantageous in long-term treatment, although this is yet to be confirmed.

Olanzapine is also an effective agent in prophylaxis, preventing both manic and depressive relapses.[41] This needs to be balanced against accumulating evidence that atypical antipsychotics such as olanzapine increase the likelihood of diabetes and hyperlipidaemia.

Psychological interventions

The other major advance in treatment of bipolar disorder has been the advent of RCTs of psychological interventions. There is now strong evidence for the beneficial role of a number of psychotherapies, including cognitive–behavioural and psychoeducational approaches (targeted towards individuals, patient groups or families).[42,43] Interpersonal and social rhythm therapy[44] (which focuses on the potentially destabilising contributions of relationship difficulties and changes to regular patterns of daily activities or sleep) has also been shown to be effective in reducing the frequency of illness episodes. These treatments have been shown to be particularly effective in reducing depressive relapse.

Such psychological therapies are designed to complement pharmacotherapies, focusing on both psychosocial precipitants and sequelae of the illness. The evidence for these psychological approaches is now of sufficient weight that they should be considered part of routine quality care.

Conclusion

The past decade has been marked by a major resurgence of scientific and community interest in bipolar disorder. However, research has highlighted a central paradox. While treatments are undoubtedly improving, it is now also being recognised that the associated disability and social impact of the disorder are high and diagnosis and treatment rates suboptimal. It is to be hoped that, in the not-too-distant future, the advent of tailored rational therapies derived from our increasing understanding of the underlying causative processes will help to remedy this. In the meantime, improved rates of diagnosis and greater utilisation of current available therapies will be critical.

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Competing interests

In the past 3 years, Philip Mitchell has received honoraria from AstraZeneca and GlaxoSmithKline for presentations. He has not served on any pharmaceutical industry advisory board during that period. Gin Malhi has served on advisory boards for GlaxoSmithKline, Wyeth, and Eli Lilly, and received honoraria from Pfizer, AstraZeneca, Organon and Lundbeck in the past 3 years. (GM has also been the recipient of an Eli Lilly Young Investigator Bipolar Research Award.)

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