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The Management of Individuals with Bipolar Disorder

A Review of the Evidence and its Integration into Clinical Practice

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Abstract

Bipolar disorder is a common, debilitating, chronic illness that emerges early in life and has serious consequences such as long-term unemployment and suicide. It confers considerable functional disability to the individual, their family and society as a whole and yet it is often undetected, misdiagnosed and treated poorly. In the past decade, many new treatment strategies have been trialled in the management of bipolar disorder with variable success. The emerging evidence, for pharmacological agents in particular, is promising but when considered alone does not directly translate to real-world clinical populations of bipolar disorder. Data from drug trials are largely based on findings that identify differences between groups determined in a time-limited manner, whereas clinical management concerns the treatment of individuals over the life-long course of the illness. Considering the findings in the context of the individual and their particular needs perhaps best bridges the gap between the evidence from research studies and their application in clinical practice.

Specifically, only lithium and valproate have moderate or strong evidence for use across all three phases of bipolar disorder. Anticonvulsants, such as lamotrigine, have strong evidence in maintenance; whereas antipsychotics largely have strong evidence in acute mania, with the exception of quetiapine, which has strong evidence in bipolar depression. Maintenance data for antipsychotics is emerging but at present remains weak. Combinations have strong evidence in acute phases of illness but maintenance data is urgently needed. Conventional antidepressants only have weak evidence in bipolar depression and do not have a role in maintenance therapy.

Therefore, this paper summarizes the efficacy data for treating bipolar disorder and also applies clinical considerations to these data when formulating recommendations for the management of bipolar disorder.

It is only to the individual that a soul is given.
Albert Einstein (1879–1955)

Bipolar disorder is currently one of the top ten public health concerns worldwide.[1] It impairs interpersonal and social development, and limits educational and vocational achievement. Individuals with bipolar disorder often develop comorbid psychological and medical illnesses, and

ultimately are more likely to commit suicide.[2,3] The symptoms of bipolar disorder usually emerge in adolescence or early adulthood,[4] and typically, it is a predictably unpredictable and recurrent illness that is characterized by periodic 'highs' and 'lows'. Therefore, the clinical management of bipolar disorder is necessarily difficult and, to date, most treatment guidelines attempt to inform complex treatment decisions simply by detailing the findings from clinical trials. Such an 'evidence base', although useful, is perhaps limited to trial populations and the findings are arguably less relevant to real-world patients. Patients in clinical practice are seldom as straightforward in terms of illness characteristics as those recruited to treatment trials, which are characterized by a raft of inclusion and exclusion criteria. Trials also have limitations with respect to study design (see section 4.1) and are further constrained by the fact that most treatment trials have a duration of weeks or a few months at most, as they are principally concerned with short-term efficacy. In clinical practice, the management of bipolar disorder is a life-long venture and, alongside quality of life, it is the overall effectiveness of treatment in reducing symptoms that matters. Another difficulty that limits the usefulness of research findings in clinical practice is that the results of such treatment studies generally describe group changes, whereas clinically, the management of bipolar disorder is a process that concerns individuals. Hence, the challenge that clinicians face is the meaningful incorporation of research trial findings into the management of individuals with bipolar disorder.

1. Aim, Method and Structure of Review

1.1 Aim

This paper advocates for evidence-based management of bipolar disorder to be considered within an individualized context. Specifically, it aims to highlight the importance of the therapeutic relationship, the need to consider the long-term adverse effects of medications when determining treatment choice, and the integration of individual-based clinical experience into the management of bipolar disorder.

1.2 Method

Using electronic databases, for example MEDLINE and PsycINFO, a comprehensive search of peer-reviewed publications was conducted regarding the treatment of bipolar disorder. Treatment guidelines and literature known to the authors were also consulted and the findings collated and reviewed. Inculcating the clinical experience of the authors, the recommendations for the management of bipolar disorder in this paper have been synthesized so as to incorporate the evidence from research studies and empirical findings from clinical practice.

1.3 Structure

The first part of the paper (section 2) provides an overview of bipolar disorder and its clinical management with phase-specific treatment recommendations. The next section (section 3) addresses the management of bipolar disorder subtypes and the treatment of bipolar disorder in different populations. A section follows this on therapeutic efficacy of treatments in bipolar disorder (section 4); this section provides a detailed review of the evidence for pharmacological treatments in bipolar disorder (section 4.1). Finally, although this section and the paper focus on pharmacotherapy, the evidence for psychological and physical treatments is also briefly reviewed (sections 4.2 and 4.3).

2. Individualizing the Management of Bipolar Disorder

2.1 Assessment

Prior to initiating treatment or considering a change of management strategy, a comprehensive and detailed clinical assessment should be undertaken where possible. Within this assessment, it is important to carefully evaluate the past psychiatric history and current mental state of the individual, and gauge the extent and severity of clinical symptoms. Ideally, this should involve a structured interview and standardized rating scales. In situations where direct assessment is

limited, the corroboration of information is critical and should be sought from medical records, family and friends. This facilitates the early integration of the family into treatment planning and delivery.

The assessment of risk to both self and others is of particular importance as is the performance of a physical examination to exclude organic causes (e.g. trauma and neurological disorders) and consequences (e.g. dehydration and toxicity) of acute bipolar illness. Vitamin D deficiency occurs commonly in patients with bipolar disorder and should also be checked at assessment.[5] The assessment should be supplemented by pertinent haematological and biochemical investigations that include urea, electrolytes and a full blood count, and check of liver and thyroid function. Where applicable, medication levels in the blood should be monitored and tests repeated as indicated. Clinical evaluation should also include an assessment of cardiometabolic health (e.g. blood sugar and lipid profile, blood pressure and body mass index) and on occasion additional specialized investigations (e.g. brain scan, lumbar puncture) may be necessary. Table I outlines the recommended investigations that should be undertaken at assessment.

Table I. Recommended baseline investigations for bipolar disorder[6]

Obtain
Personal and family medical history, especially history of metabolic and cardiac disease
Perform
Full blood count
Blood chemistry analyses:
electrolytes
serum creatinine (including 24-hour creatinine clearance)
thyroid stimulating hormone
liver function tests
Urinalysis
Hormone assays, e.g. prolactin levels (if indicated)
Assessment of metabolic syndrome:
waist circumference
body mass index
blood pressure
fasting lipid profile (triglycerides, HDL-C, LDL-C)
fasting blood sugar
Screen
Vitamin deficiency
Substance use
urine toxicology (if indicated)
Polycystic ovarian syndrome
reproductive endocrine abnormalities (if prescribing valproate to females of child-bearing potential)
Pregnancy test (if indicated, especially if prescribing valproate or carbamazepine)
Infectious diseases (if indicated)
Examine
Extrapyramidal side effects: clinical assessment of abnormal involuntary movements
Cataracts: ocular examination (if prescribing quetiapine)
Tests
ECG (if prescribing lithium and age >40 years)
EEG (if indicated)
If indicated, MRI (preferred)/CT

CT = computed tomography; **ECG** = electrocardiogram; **EEG** = electroencephalogram; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **MRI** = magnetic resonance imaging.

2.1.1 Onset of Bipolar Disorder and Accurate Diagnosis

Mania is the hallmark of bipolar disorder. In its classic form, full-blown mania is easily recognized; however, in most patients, the onset of bipolar disorder is insidious. Typically, the illness heralds its onset with only minor fluctuations in mood that can last for days and sometimes weeks prior to eventually crystallizing into clinical depression.[7] Similarly, manic episodes are often preceded by a brief period of heightened energy and elevated mood along with racing thoughts and a diminished need for sleep.[8] The symptoms and signs that occur during these 'ramping up periods', in which there is an indication of what is likely to eventuate, are called early warning symptoms (EWS), and in practice these indicate a need to adjust management. However, not all patients with bipolar disorder have clearly defined EWS, and many lack a prodromal period of mood instability.[9] Diagnostically, bipolar disorder is defined on the basis of mania or hypomania, even though it is the depressive phase of the illness that confers the greatest burden.[10] Therefore, as individuals with bipolar disorder usually present with depressive symptoms, they are often initially diagnosed as having major

(unipolar) depression and treated accordingly. Consequently, many individuals with bipolar disorder receive insufficient and sometimes inappropriate treatment.[11]

Misdiagnosis is further complicated by the context within which bipolar symptoms emerge. The clinical picture usually begins to take discernible form during adolescence; however, this is a time of significant physiological change because of brain growth and maturation that involves cognitive, social and emotional development.[12] Identifying bipolar signs and symptoms within this changing milieu is necessarily problematic; although a family history of bipolar disorder, atypical depressive or psychotic features, and a lack of response to antidepressant treatment are potentially useful indicators.[13] As yet, there is no reliable clinical or biological bipolar disorder marker and, therefore, in practice a significant proportion of patients with the illness are missed or misdiagnosed.

2.1.2 Bipolar Subtypes and Bipolar Spectrum

The Diagnostic and Statistical Manual of Mental Disorders (4th Edition), text revision (DSM-IV-TR)[14] divides bipolar disorder into 'bipolar I', 'bipolar II', 'cyclothymia' and 'bipolar disorder not otherwise specified' but, in reality, the latter two 'categories' are seldom used. The range of diagnoses implies a spectrum of bipolarity that perhaps encompasses personality,[15] and it has been suggested that this 'bipolar spectrum' extends further to include unipolar (major) depression.[16] In practice, many patients with 'manic' bipolar presentations do not strictly fulfil the necessary duration or severity criteria for mania, or indeed hypomania, and yet clinically they have significant mood disturbance in keeping with bipolar disorder. These 'soft' bipolar diagnoses are difficult to define categorically, but are thought to have an estimated prevalence twice that of bipolar I and II disorder. Recent statistics suggest that bipolar I and II disorder have equivalent lifetime (1.0% and 1.1%) and 12-month (0.6% and 0.8%) prevalence with subthreshold bipolar disorder (spectrum) adding a further 2.4% and 1.4%, respectively.[17]

Therefore, a significant number of patients have symptoms that bridge the diagnostic boundary between unipolar and bipolar depression and, similarly, bipolar individuals with psychotic symptoms extend through schizoaffective disorder into schizophrenia.[18] This broadening of bipolarity necessarily complicates its diagnosis and management because relatively little is known about the course and response to treatment of bipolar spectrum disorders.

2.1.3 Mixed Episodes and Co-Morbidity

A common presentation, and further complication in the diagnosis of bipolar disorder, is the occurrence of an admixture of depressive and manic symptoms.[19] These presentations are described as 'mixed'. In the DSM-IV, a mixed episode simultaneously fulfils the criteria for both a depressive and manic episode, and usually manifests as the intrusion of manic symptoms into a largely depressive presentation or the emergence of depressive symptoms within a predominantly manic picture. But DSM-IV requirements for a mixed episode have been criticized for their high threshold and failure to account for the subsyndromal depressive symptoms that often accompany a manic episode.[20] Furthermore, many other variants of mixed states are not captured by DSM-IV and, in practice, they are difficult to detect and adequately treat, particularly in the context of bipolar II disorder.[21] Clinically, mixed episodes occur in up to 40% of hospital admissions of bipolar disorder[22] and are associated with greater Axis I co-morbidity, including substance abuse disorders, a higher risk of suicide, catatonic symptoms and poorer treatment outcome than pure manic or depressive episodes.[23,24] Mixed episodes clearly contribute to the high rate of co-morbidity found in bipolar disorder with concurrent anxiety disorders (42–93%) or substance misuse problems (42–71%) tending to be the norm.[17,25,26]

2.1.4 Course of Bipolar Disorder and Rapid Cycling

A number of longitudinal studies[27-32] have demonstrated that recurrence is linked to premorbid functioning and can be potentiated by a number of factors such as hypothyroidism,

substance abuse and antidepressants.[33] In the DSM-IV, increased cyclicity with four or more episodes of mania, hypomania or depression over a period of 12 months or less is described as 'rapid cycling'[34] and, in this definition, episodes of illness must be demarcated by either complete or partial remission of symptoms (for at least 2 months) or a switch to opposite polarity.[14] Consequently, rapid cycling is considered both a 'subtype' and 'course specifier' of bipolar disorder. However, as the cycle length diminishes, and rapid cycling tends to 'ultra-rapid' and 'rapid-ultradian' forms, the clinical picture melds into that of mixed states.

Overall, 10–20% of patients with bipolar disorder have a rapid-cycling pattern of illness[35] that favours women[36,37] and is more likely to occur later in life (>40 years of age). However, it remains unclear whether rapid cycling is a distinct subtype of bipolar disorder, although diminished responsiveness to treatment and a greater risk of suicide suggests some separation. Clinically, rapid-cycling bipolar disorder clearly confers greater morbidity than non-rapid-cycling presentations and is associated with higher rates of co-morbid substance misuse and hospitalization.[38,39]

2.2 Formulating Treatment Recommendations

2.2.1 General Principles

In practice, the management of bipolar disorder cannot be easily compartmentalized according to phases of illness and, therefore, some general principles that can be used clinically are briefly considered, prior to discussing stage-specific therapeutic recommendations. However, it is important to note that these principles are dependent upon the existence of functional therapeutic relationships that provide a conduit for all therapy and are the cornerstone of clinical management. It is, therefore, apt that the fundamentals of treatment that need to be considered in the management of bipolar disorder are captured by the acronym 'RELATION' (Range of Effective Long term Approaches Tailored to Individual Outcomes and Needs). This tailored long-term approach is explicated in table II and is necessary for optimal outcome. The collective aim of the principles that underpin this approach is to ensure that an iterative balance is achieved during management. Specifically, due consideration is given to a broad range of therapies for bipolar disorder while maintaining a focus on the specific needs of the individual.

Table II. 'RELATION': key considerations in the long-term management of bipolar disorder

Range of effective treatments
In addition to pharmacotherapy, it is useful to consider multiple strategies when formulating a treatment plan and to maximize both their specific and facilitatory role. To do this, the timing of interventions, such as psychological therapies, is critical and successful implementation necessitates preparation. It is, therefore, important to plan management early in the course of the illness so as to ensure the timely and effective commencement of therapies. A good example of such a strategy is the combination of CBT with pharmacotherapy set against a background of greater understanding of the illness through education
Long-term approaches
When initiating pharmacotherapy for the acute phases of illness, it is essential to give consideration to maintenance therapy and incorporate into the decision-making process the long-term consequences of medication. Of particular importance are issues of tolerability and adverse effects that can become severe and debilitating, and thereby limit adherence to treatment. In most clinical settings, the acute symptoms of bipolar disorder are usually the focus of treatment strategies and, although the current mental state is clearly of salience, it is equally important to bear in mind the long-term aspects of the illness
Tailored to individual outcomes and needs
Consideration should be given to the individual's unique circumstances and expectations. The historical pattern of bipolar disorder, in particular its periodicity and responsiveness to treatment, is often indicative of future outcome and, along with co-morbidity and family history, should inform the management plan. In complex cases, detailed charting of past episodes and treatments can also be helpful. Treatment needs to be integrated into the person's individual lifestyle, personality and social circumstances

CBT = cognitive behavioural therapy.

2.2.2 Acute Phases

Clinical assessment of an individual presenting with acute manic or depressive symptoms should gauge the severity of symptoms, level of functional impairment, degree of insight, evidence of psychosis, risk to self and others, and availability of family and/or community support. This information will influence treatment considerations such as ability to give informed consent, capacity to make rational decisions, the deployment of an

appropriate care model according to least restrictive practice and prescribed mode of treatment administration. In this regard, the patient may require involuntary admission to hospital to receive treatment, agree to a voluntary admission or receive community-based treatment. Important considerations are the likelihood of self-harm and, since insight is often compromised in the manic phase of bipolar disorder, it is important not to rely solely on self-report in instances of uncertainty but to seek corroboration from family and significant others. Furthermore, prior to making changes to prescribed medication, it is important to check compliance with medication because in many cases it is non-adherence to treatment that has precipitated an acute relapse.

Mania

The focus of treatment is to quell the acute symptoms of mania and to manage any accompanying behavioural disturbance. There is a wide range of agents with a substantive evidence base that warrant indication as a first-line treatment. In addition to lithium and valproate, these include the atypical antipsychotics and combinations of lithium or valproate with an atypical antipsychotic. Short-term use of the latter combination strategies can achieve greater efficacy and assist with psychotic and/or behavioural symptoms. Alternatively, benzodiazepines can be used adjunctively for brief periods to assist with the management of behavioural disturbance.

First-line agents are effective in almost 50% of patients within 3 weeks but if significant improvement is not evident within the first fortnight, despite appropriate dosing and compliance with a particular agent, switching to another first-line agent should be considered. In patients with a partial response, a higher dosage may be warranted prior to combining or switching. In instances where treatment has been commenced with lithium or valproate monotherapy, combination treatment usually involves the addition of an antipsychotic medication. However, if the patient is already receiving a combination of agents, then one or both of the medications can be switched in sequence.

Second-line agents that include established medications such as haloperidol and carbamazepine are most likely to be equally effective as first-line agents. However, they are considered second-line options largely because of poor tolerability or a lack of sufficient data. If typical antipsychotics are used to successfully treat a manic episode, their long-term use should be curtailed because they are likely to precipitate depressive symptoms.

Bipolar Depression

Unlike acute mania, the evidence base to guide treatment recommendations for bipolar depression is less definitive and successful treatment is likely to require a broader, multi-modal approach that incorporates adjunctive psychological interventions in particular. Mania probably has a more pure biological foundation, whereas the variance of the aetiology of depression includes biological, social, psychological, personality and lifestyle factors, all of which form potential intervention targets. There is no evidence base for psychological therapy of acute bipolar depression; however, on the basis of its efficacy in unipolar depression and in bipolar maintenance treatment, it is a rational option. The decision of when to commence psychological therapy varies and is dependent upon the severity of depressive symptoms and individual preference. However, the putative role of psychological interventions in the management of bipolar disorder should be considered at the outset, as part of the initial treatment plan.

First-line pharmacological treatment options for the monotherapy of bipolar depression include lithium, valproate and quetiapine. Olanzapine and lamotrigine monotherapy fail to qualify because the observed clinical changes are extremely small and lack salience. Hence, along with other anticonvulsants and antipsychotics such as carbamazepine and aripiprazole, respectively, these are regarded as second- or third-line options, after having considered combinations. First-line medication combinations include olanzapine plus fluoxetine (OFC) or lithium combined with valproate or lamotrigine. All are efficacious; however, each agent has unique

advantages and disadvantages in relation to clinical effectiveness, speed of antidepressant action and tolerability. Furthermore, suicide prevention, where lithium has distinct advantages, and prophylactic properties should also be given consideration when determining treatment choice. Patients who have breakthrough depression[7] whilst receiving first-line treatment options should have their medications optimized. This involves ensuring compliance and monitoring medication blood levels where possible.

The efficacy of antidepressants in the treatment of bipolar depression remains unclear and data from unipolar depression provide little assistance.[40] The three largest and most methodologically rigorous trials of antidepressants (paroxetine, paroxetine or bupropion, and agomelatine) were all negative. However, antidepressants may still benefit a small cohort of patients with bipolar depression; if used, they should ideally be administered in conjunction with an antimanic or maintenance agent to limit mood instability.

2.2.3 Maintenance Treatment and Relapse Prevention

Lithium is still viewed as the mainstay of prophylaxis in bipolar disorder, although it is more effective in preventing manic relapses than depression. In contrast, lamotrigine has been shown to be more effective in the prevention of depressive episodes. Considering the antipsychotics, a number appear to demonstrate varying maintenance properties including quetiapine, olanzapine and aripiprazole. Amongst these, quetiapine appears to have equivalent efficacy in preventing both manic and depressive episodes, whereas all other atypicals show greater efficacy in mania than depression. Similarly, ziprasidone and risperidone also seem to have potential prophylactic properties; however, as yet, no atypical antipsychotic has reliably demonstrated, in a valid and well designed, long-term, maintenance study, efficacy compared with placebo. Therefore, no agent from this class of medications faithfully fulfils the requirements of an archetypal mood stabilizer. This is critical because bipolar disorder, as already discussed, is a recurrent illness with the majority of patients experiencing relapses throughout their lives. It is the prevention of further episodes that is of importance to individuals with bipolar disorder because it is the acute episodes that result in hospitalization, suicide and loss of functionality. Maintenance of well-being is therefore of paramount importance and, in this regard, many agents lack the necessary suitability in terms of efficacy and tolerability for long-term adherence to treatment. In addition to prophylaxis, namely the prevention of further episodes of illness, maintenance treatment should manage subsyndromal symptoms because these confer considerable morbidity. In this respect, it is equally important that maintenance agents do not add to the burden of the illness by way of adverse effects.

In general, agents that have been successful in the treatment of acute episodes tend to be continued into maintenance therapy and, hence, there is a need for the consideration of prophylaxis when prescribing medications for acute episodes. The predominance of polarity has been suggested as an indicator of future episodes. In this regard, agents such as lamotrigine, lithium and quetiapine are perhaps better for the prevention of depressive relapse than other first-line choices. Conversely, all first-line agents with the exception of lamotrigine can be considered for the prevention of manic episodes. However, in maintenance therapy, perhaps more important than the specific medication is the need to establish a therapeutic relationship.[41,42] The monitoring of both symptoms and treatment response is critical in the prophylaxis of bipolar disorder, and it is in this phase of the illness that 'successful management' achieves overall recovery. In this context, psychological interventions play an even more important role than in managing acute illness.

Psychological interventions are a key component of the long-term management of bipolar disorder, and can assist in improving engagement, helping to understand the patterns of illness, identifying relapse signatures, improving functioning and, ultimately, reducing the risk of relapse. Specific interventions that have demonstrated benefit in bipolar disorder include cognitive behavioural therapy (CBT), interpersonal and social rhythm

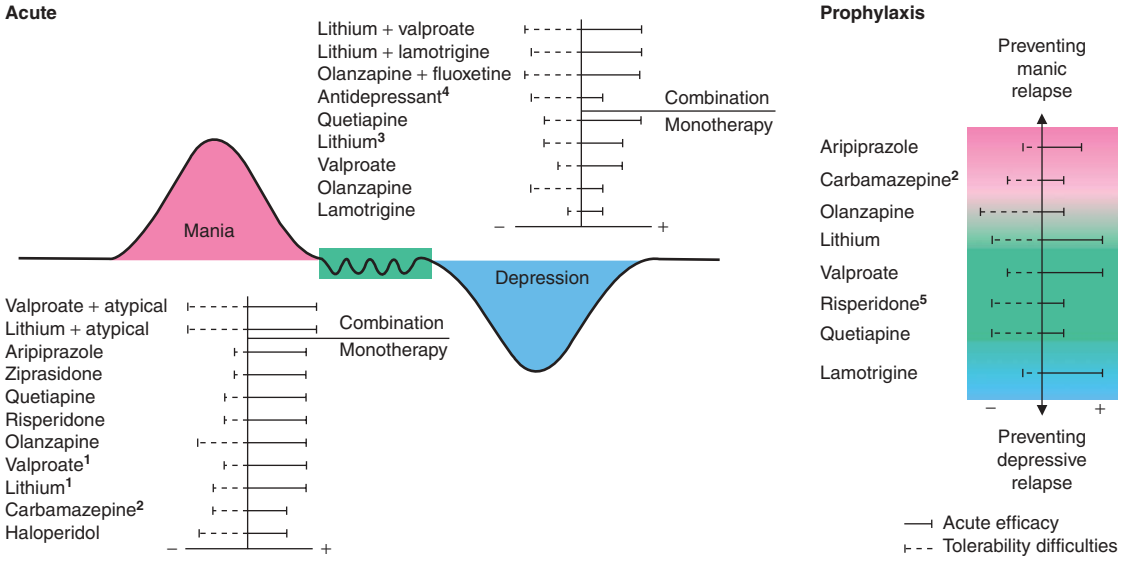

Fig. 1. Overview of efficacy and tolerability ratings for pharmacological treatments commonly used in bipolar disorder. This figure captures the relative merits of agents in terms of efficacy and tolerability. The top and bottom schematics deal with the acute (mania and depression) and maintenance phases of bipolar disorder, respectively. The joint presentation of the relative efficacy and tolerability for each agent provides a useful guide as regards effectiveness in clinical practice. Tolerability ratings have variable impact depending on duration of treatment and urgency of need for treatment. Therefore, they are of greater importance in prophylaxis than in the acute treatment of mania or depression. **1** While the efficacy of agents are comparable to antipsychotics, lithium and valproate can be slower to take clinical effect; **2** slow-release formulation is better tolerated; **3** there can be a 6- to 8-week delay in antidepressant effect; **4** adjunctive; **5** no randomized controlled trial data available, rating based on open-label studies. + indicates good efficacy; – indicates poor tolerability.

therapy (IPSRT), family-focused therapy (FFT) and group psychoeducation.[43,44] However, commencement of psychological programmes early in the course of the illness seems to be important in order to achieve better outcomes.[45] Therefore, where possible during the maintenance phase of illness, psychological therapy should be offered adjunctively to all patients with bipolar disorder (figure 1).

3. Managing Subtypes and Different Presentations of Bipolar Disorder

3.1 Bipolar II Disorder

Research data specifically focusing on patients with bipolar II disorder are limited and, therefore, recommendations for the management of bipolar II disorder are largely based on open-label trials, *post hoc* analyses or trials with heterogeneous subject groups consisting of bipolar I and II disorder.

As it is by definition mild, brief and not impairing, in reality, hypomania is seldom a target of direct treatment, and is usually simply a diagnostic marker.[46] Treatment of bipolar II disorder is essentially the treatment of bipolar depression. In the absence of evidence for the treatment of hypomanic episodes, it is recommended to follow evidence-based guidelines for acute manic episodes. Consequently, hypomania may be treated with lithium, valproate or one of the atypical antipsychotics, either as monotherapy or in combination. Since there is reasonably strong evidence for lithium use in the maintenance phase of bipolar II disorder,[47,48] it has been suggested that lithium may also be a reasonable choice for acute treatment, especially when it is anticipated that the same treatment should be continued for prophylaxis.[49]

In bipolar depression, randomized controlled trials (RCTs) from the BOLDER (BipOLar DEpRession) studies[50,51] and EMBOLDEN (Efficacy of Monotherapy seroquel in BipOLar DEpressioN) data[52,53] have demonstrated the

efficacy of quetiapine in treating both patients with bipolar I and II depression. Furthermore, a *post hoc* analysis of patients with bipolar II depression from the two BOLDER studies (n = 351) demonstrates the efficacy of quetiapine as monotherapy.[54] Small RCTs that have included patients with bipolar II depression have demonstrated benefit over placebo for adjunctive pramipexole[55,56] and modafinil.[57] Furthermore, open-label findings provide some support for the use of lithium, lamotrigine and valproate in bipolar II depression.[58,59]

There is an ongoing debate about the efficacy of antidepressants in bipolar depression and the associated risk of precipitating hypomanic episodes (see also section 4.1.4). While some large trials (e.g. STEP-BD [Systematic Treatment Enhancement Program for Bipolar Disorder]) that have included both bipolar I and II patients have not reported any additional benefit of adding an antidepressant to treat bipolar depression,[60] there are limited data to support the use of antidepressant monotherapy in patients with bipolar II depression.[61-64] Furthermore, the risk of switching may be lower in bipolar II than bipolar I disorder.[65]

With regard to maintenance interventions, lithium has the strongest evidence base for the treatment of bipolar II disorder,[47,48] followed by lamotrigine.[66] Therefore, these agents may be considered the best first-line options for the maintenance of bipolar II disorder.

Studies assessing the efficacy of psychotherapeutic interventions in bipolar II disorder are sparse and usually consist of heterogeneous cohorts including unipolar depressed and/or subjects with bipolar I disorder. In studies of bipolar I and II disorder, there is some support for interventions that focus on the identification of EWS;[67] however, there are no specific treatments that target bipolar II disorder.

3.2 Mixed States

Mixed states are predictive of a worse response to pharmacological treatment, particularly lithium, where it is reported that up to 60–70% of patients with a mixed episode have an inadequate response.[68] Most trials for acute mania include patients with mixed states; however, there are few studies that have specifically investigated mixed states in bipolar disorder. Therefore, recommendations for the treatment of mixed states closely overlap those for acute mania.

Of the available data specific to mixed states, the strongest evidence exists for olanzapine and valproate as monotherapy, or in combination.[23,69,70] However, in practical terms, the risks of metabolic syndrome with olanzapine limit its use long term. Lithium appears to be less effective in mixed states[69] and is, therefore, not optimal as monotherapy; however, carbamazepine may be beneficial for prophylaxis, particularly with regard to depressive relapse.[71] Of the atypical antipsychotics, olanzapine has the largest evidence base to support its use in mixed states;[23] however, subsets of patients with mixed states in RCTs have also demonstrated benefit over placebo with ziprasidone,[72] aripiprazole[73] and, with regard to manic symptoms, risperidone.[74]

Antidepressant use in mixed episodes is complicated by an increased risk of switching to mania and is not generally recommended.[75] Antidepressant-induced mania is more likely to be mixed than euphoric. Antidepressants should generally be discontinued in individuals with mixed states.

3.3 Rapid Cycling

Patients presenting with rapid cycling are more difficult to treat and have a poor treatment response.[33,38] Pharmacotherapy appears to be more effective in treating mania compared with depressive symptoms;[33] therefore, refractory depression is a more common complaint in rapid-cycling bipolar disorder.[76]

With limited prospective, controlled treatment trials for rapid cycling, there is no consensus as yet for its optimal treatment and, although lithium was once thought to be inferior in treating rapid cycling, it is now recognized that the reduced response is not specific to one agent.[38] Indeed, lithium and valproate, agents that arguably have the largest evidence base in rapid-cycling bipolar disorder,[76-79] have generally been lacklustre in terms of efficacy in this subtype

of the illness. Furthermore, lamotrigine, although putatively of benefit in treating depressive symptoms in conjunction with lithium or valproate[80] or as monotherapy in bipolar II disorder,[66] has not been consistent in achieving a response.[81] The efficacy data of atypical antipsychotics in rapid-cycling bipolar disorder are limited and much of the data rely on the inclusion of rapid-cycling patients in mania and bipolar depression efficacy trials. Nonetheless, the data are promising, suggesting atypical antipsychotics may have a useful role in the treatment of rapid cycling.[39,73,82-85] As with mixed states, where possible, antidepressants should be avoided in rapid-cycling bipolar disorder. If required, their use should be of limited duration so as to minimize the risk of precipitating a switch into mania.[86]

In practice, the use of combination treatments that have only a limited evidence base is often necessary to effectively manage the manic and depressive components of the illness. Open-label data from an extension of a controlled trial found marked antimanic but modest antidepressant effects when lithium and valproate were combined.[76] Because of a tendency to produce an antidepressant effect, lamotrigine has been suggested as a reasonable adjunctive treatment option, although this is yet to be evaluated.[80] A 3-year crossover trial of lithium, carbamazepine and a combination of the two, each of 1-year duration, found that patients with rapid-cycling bipolar disorder had significantly higher response rates on a combination of lithium and carbamazepine (56%) compared with either agent alone (28% for lithium and 19% for carbamazepine).[87] However, overall evidence for combination strategies is weak and more research is required.

Finally, although based on open-label studies and case reports, electroconvulsive therapy (ECT) appears to be a reasonable treatment option for patients with rapid-cycling bipolar disorder who have not responded to alternative treatment options.[88]

3.4 Co-Morbidities

Despite a high prevalence in clinical presentations, there is generally a paucity of data to guide the specific management of co-morbidity in bipolar disorder.[89,90] In co-morbid anxiety, small RCTs or open-label trials of quetiapine have demonstrated some benefit in treating anxiety symptoms in bipolar I depression,[91] and olanzapine or lamotrigine added to lithium maintenance treatment has been shown to improve anxiety.[92] Interestingly, antidepressants, particularly serotonin reuptake inhibitors (SRIs), although established and effective in the treatment of anxiety disorders, remain contentious with respect to their use in treating bipolar disorder (see section 4.1.4 for further discussion).[40] Somewhat surprisingly, relatively little data have been acquired on psychological interventions; however, in lieu of extant evidence, it is clinically reasonable to consider adding CBT[93] to existing pharmacological treatments. Mindfulness-based cognitive therapy (MBCT) has shown promising results in a pilot RCT for co-morbid anxiety and bipolar disorder.[94] See section 4.2 for further detail on the application of psychological treatments in bipolar disorder.

When treating co-morbid substance misuse, it is considered good practice to treat both psychiatric and substance misuse conditions concurrently, irrespective of mood state. With regard to pharmacological interventions, in one RCT, valproate added to lithium provided additional benefit over placebo to reduce heavy drinking in patients with bipolar disorder,[95] and in adolescents, lithium was superior to placebo in treating adolescents with co-morbid bipolar disorder and substance use disorder.[96] Open-label trials have reported some benefits on mood and drug cravings with adjunctive quetiapine[97] or lamotrigine.[98] There is weak empirical evidence to support the integration of pharmacological and psychotherapeutic interventions specifically in bipolar disorder with co-morbid substance misuse;[99] however, a recent review identified the following strategies as effective in treating patients with a dual diagnosis: motivational interviewing, CBT, contingency management, relapse prevention, case management, social-skills training and modified 12-step programmes.[100]

3.5 Special Populations

Treatment recommendations for specific populations with bipolar disorder do not differ

markedly from mainstream recommendations. However, they are based on a more limited evidence base and, as such, warrant greater caution and consideration of concurrent treatments, comorbid conditions and psychosocial factors that may impact on management.

In young people, the diagnosis of bipolar disorder is surrounded by controversy and is complicated by a greater occurrence of 'atypical' presentations[101,102] along with the added impact of the developmental context, contributing psychosocial stressors and potential co-morbidities (e.g. attention-deficit hyperactivity disorder, conduct disorders, substance misuse, depression, anxiety and emerging personality disorder).[103] With regard to treatment, there are a lack of controlled data to allow for clear recommendations in young people, and evidence is limited mostly to open-label trials or extrapolations from the adult literature. Therefore, recommendations for pharmacological management generally reflect that of the adult population, but are provided with caveats and cautionary notes. Engagement, alliance and adherence are particular priorities in young people with the disorder.

In general, it is considered good practice that pharmacotherapy be delivered in combination with psychosocial interventions. In particular, there is promising evidence emerging for FFT,[104] CBT[105,106] and psychoeducation for both the young person and their family members.[107,108] There is a suggestion that both CBT and psychoeducation are more efficacious if used earlier in the illness. Valproate has been associated with an increased risk of polycystic ovarian syndrome (PCOS) and females of child-bearing potential should be monitored for reproductive-endocrine abnormalities (menstrual cycles, body weight and symptoms of hyperandrogenism).[109] For detailed recommendations in managing bipolar disorder in young people, recent practice guidelines specific to this population should be consulted.[110,111]

In elderly patients, medications generally need to be titrated more slowly and conservatively because treatment decisions need to take into account age-related increases in the likelihood of drug interactions, sensitivity to adverse effects and rates of medical co-morbidities, and the potential changes in pharmacokinetics and pharmacodynamics that occur in the elderly.[112,113] Evidence for the use of psychological interventions in elderly patients with bipolar disorder is lacking, with empirical data, drawn largely from adult studies, suggesting that it is likely to be of benefit in older adults.[112]

Treatment decisions during the perinatal period should be determined following careful consideration of the risks and benefits to both the mother and infant. Risks associated with exposure to psychotropic drugs need to be carefully balanced against the risk of untreated mental illness. Interventions should consider the mother and child together, as well as the broader psychosocial context, and a collaborative relationship between all support services represents good clinical practice.[114] There is also a high risk of relapse in this population, and pregnant patients may require more regular monitoring of mood symptoms during pregnancy and the postnatal period.

Data on the use of psychotropic medication during the perinatal period are limited and vary, depending on the type of drug, its timing in pregnancy, breast-feeding status and dose. A detailed review of this information is beyond the scope of this paper and publications that provide specific guidance in managing bipolar disorder during the perinatal period should be consulted.[114-119]

Many medications that are commonly used in bipolar disorder pose a risk to the unborn fetus or newborn through breastfeeding. Of particular note, valproate exposure during the first trimester of pregnancy is associated with an increased risk of fetal abnormalities (risk increased from 6 per 10 000 in the general population to 100–200 per 10 000 with valproate), including neural tube defects, and should be avoided where possible in women who are pregnant or are likely to become pregnant.[114,117] Valproate use in pregnancy is also associated with lower intelligence quotient among offspring compared with lamotrigine.[120]

Carbamazepine exposure in pregnancy is associated with fetal carbamazepine syndrome, although it is unclear whether it increases the risk of fetal neural tube defects or developmental

delay.[117] Lamotrigine appears to have a more favourable risk profile than valproate and carbamazepine, and is less likely to increase the risk of major malformations, although it may increase the risk of facial clefts.[117,121]

Lithium exposure may be associated with an increased risk of congenital heart defects during the first trimester of pregnancy and a neonatal toxicity called 'floppy-baby syndrome'.[114,117] However, the extent of this risk remains unclear. Lithium is therefore not recommended for routine use in pregnancy, particularly in the first trimester and during breastfeeding; however, it may be continued during pregnancy when the risks of cessation that may lead to relapse are considered to outweigh the risks associated with ongoing use.

Antipsychotics appear to be safer than lithium and anticonvulsants, with most safety data available for typical antipsychotics.[122] There are few data available for atypical antipsychotics; however, there are no known major increases in fetal abnormalities associated with their use.[123]

Meta-analyses of SRIs suggest that the risk of major malformations associated with SRIs (fluoxetine, sertraline, citalopram, escitalopram) is no more than the base rate of 1–3%.[124,125] Although usually mild, SRIs are associated with a risk of withdrawal or toxicity in neonates. Increased rates of persistent pulmonary hypertension in the neonate have been reported when taken after 20 weeks' gestation.[114,126] Antidepressants have been measured in breast milk with breastfeeding infants exposed to doses per kilogram bodyweight <5% of the maternal dose for sertaline, fluvoxamine and paroxetine, and <10% of the maternal dose for fluoxetine, citalopram and venlafaxine.[127]

For women with bipolar disorder considering becoming pregnant, a treatment plan is recommended and should be agreed upon after frank and open discussions between the woman and her treating physician. In most cases, discontinuing medication is an unsuitable option.

Despite limited controlled data, ECT is considered to be safe and effective for patients with severe bipolar disorder across all age groups, including the elderly, the young and during the perinatal period.[128-131]

4. Therapeutic Efficacy of Treatments for Bipolar Disorder

In recent years, the therapeutic armamentarium for bipolar disorder has expanded considerably both in terms of pharmacological and psychological options. Hence, the clinical management of bipolar disorder now usually involves a combination of medications and psychological interventions. Physical treatments, such as ECT, can also be used; however, given that its use is less frequent and less widespread, its use is not discussed in detail here.

Pharmacotherapy is used both for acute exacerbations of bipolar disorder and for prophylaxis. Individual medications can therefore be classified according to their putative pharmacological action, for example antidepressants, or their putative role in the management of bipolar disorder, such as maintenance therapies. However, it is important to note that in the context of bipolar maintenance the terms prophylaxis and relapse prevention differ, as do the studies used to assess treatment. Generally, prophylaxis trials involve the treatment of patients who have been stable for a significant period of time following recovery from a mood episode. These euthymic patients are included irrespective of their last episode and the study drug is essentially used to assess efficacy in preventing new mood episodes. In contrast, studies that assess relapse prevention involve patients who, following an acute mood episode, first undergo open-label treatment to the point of recovery and are then randomized to continue active treatment or switch to placebo. This study design, also referred to as 'enriched', is increasingly used in RCTs; however, the results of such enriched studies are less widely applicable compared with studies that assess prophylaxis. One of the reasons for this is that continuation and maintenance treatments have potentially different starting points depending on the study design. Conventionally, the continuation phase of treatment is the period of 2–6 months following recovery, during which time the illness is still putatively active and worsening symptoms suggest relapse. After 6 months of recovery and resolution of the acute episode, maintenance begins and the

recurrence of symptoms indicates the onset of a new episode of illness. Therefore, in a study with an enriched design, improvement in the first 6 months may actually reflect efficacy in relapse prevention as opposed to genuine prophylaxis because much of this period is in fact continuation as opposed to maintenance.[6] Conversely, studies with an enriched design can lead to a perceived increase in placebo-related relapse when effective treatment is withdrawn. This in turn can result in an overestimate of therapeutic benefit. The latter has also occurred within the psychiatric bipolar literature because of an inherent publication bias towards studies that have positive results. In general, trials that are negative or only show an effect on secondary outcome measures are either not published or are published in journals with less impact and widespread circulation. Recently, unpublished data have come under scrutiny, and inclusion of findings from all studies related to a particular agent have often led to a reappraisal of its efficacy and clinical benefit.[81]

In this section of our review, the evidence for each of the treatments used in bipolar disorder is reviewed in detail. However, the practical use of medications in a clinical context has been considered according to the phase of illness in previous sections.

4.1 Pharmacological Options

In recent years, there has been a resurgence of interest in defining both the phases of bipolar illness (mania, hypomania, depression, euthymia, mixed) and their response to treatment (response, remission, recovery, switch). In conjunction with this discourse, there has been renewed debate as to 'what defines a mood stabilizer?'.[132,133] In this regard, lithium is perhaps the only agent that approximates to the most stringent definition of a mood stabilizer, which requires an agent to have an effect upon depressive and manic phases of bipolar disorder both acutely and in the long term. However, in practice, many clinicians also regard the anticonvulsants valproate, carbamazepine and even lamotrigine, as mood stabilizers and some of the atypical antipsychotics are increasingly being placed in the same frame.[134]

In this article, we have adopted a more traditional, perhaps conservative view and grouped medications according to their primary pharmacological action and limited the term 'mood stabilizer' to three agents, namely lithium, valproate and carbamazepine. Furthermore, where possible, we have identified the specific action of an agent rather than using the broader description of stabilizing mood. The strength of evidence for each medication, or combination of medications, are summarized and tabulated according to each phase of bipolar disorder (table III).

4.1.1 Lithium

Acute Mania

Since its initial discovery by John Cade,[138] lithium remains the benchmark treatment for acute mania.[139] Many earlier studies demonstrating the superiority of lithium over placebo[140-143] were limited methodologically in that they used crossover designs or non-randomized allocation. More recently, a review of trials spanning 30 years has reaffirmed its effectiveness in acute mania[135] and lithium is still regarded as the 'gold standard' comparator when trialling other medications.

Bipolar Depression

Surprisingly, the acute antidepressant effect of lithium monotherapy has not been firmly established,[144,145] yet lithium maintains a prominent role in most treatment guidelines perhaps largely because of expert preference.[103] Early trials demonstrating the superiority of lithium over placebo[142,143,146-152] comprised mainly of small crossover studies of short duration and these have been widely criticized for their abrupt cessation of lithium prior to entering the double-blind phase, because this is thought to have contributed to an elevated relapse rate in the placebo group.[7]

A unipolar depression meta-analysis[148,151,153,154] indicates that lithium is superior to placebo.[155-160] In these studies, bipolarity or a family history of bipolar disorder predict a better outcome to lithium and its efficacy is thought to be best demonstrated in the treatment of 'classic bipolar disorder'.[161,162] However, recent findings from the EMBOLDEN I trial fail to separate lithium (600 mg/day) and placebo in the acute

Table III. Summary of evidence for pharmacological treatments in bipolar disorder

Treatment	Acute mania	Bipolar depression	Maintenance
Lithium	+++	++	+++
Anticonvulsants			
valproate	+++	++	+++
lamotrigine		+	+++
carbamazepine	++	+	+
oxcarbazepine	+[a]		+[a]
phenytoin	+		+
gabapentin			
topiramate			
Antipsychotics			
olanzapine	+++	+[b]	+
quetiapine	+++[c]	+++[c]	+
risperidone	+++		+[a]
aripiprazole	+++	+	++[d]
ziprasidone	+++		+[e]
other atypicals	+[f]		+[f]
typical	++[g]		
Antidepressants		+[h]	
Combinations			
valproate + atypical	+++[i]		
lithium + atypical	+++[j]		
lithium + valproate		+++	[k]
OFC		+++	
lithium + lamotrigine		+++	

a Adjunctive treatment.

b Clinical improvement seen mainly in neurovegetative symptoms (sleep, appetite) and not in mood.

c Data for extended-release quetiapine, currently published in abstract form, also appear to be promising.[135-137]

d Primarily for preventing mania.

e Abstract data.

f Clozapine and adjunctive asenapine.

g Short- and long-term tolerability of typical antipsychotics has meant that despite proven efficacy their use is diminishing.

h Evidence for adjunctive antidepressant remains equivocal, OFC has strong evidence.

i Risperidone, olanzapine, quetiapine or aripiprazole.

j Quetiapine, based on abstract data.

k Preliminary data are promising, suggesting that this combination is better than either lithium or valproate alone.

OFC = olanzapine fluoxetine combination; + indicates weak or emerging evidence; ++ indicates moderate evidence; +++ indicates strong evidence.

treatment of bipolar depression,[52] although this may be a function of low plasma lithium levels (<0.8 mmol/L). The latter has been shown to be an important determinant of efficacy.

In practice, most clinicians are reluctant to use lithium alone as an antidepressant[103] and regard it predominantly as an antimanic agent with prophylactic properties.[163] However, overall lithium has demonstrated efficacy in treating acute bipolar depression and, therefore, many guidelines continue to advocate its use first-line.[110,164-166]

In contrast, the efficacy of lithium as an augmentation strategy to antidepressants is less controversial, and has been demonstrated in both unipolar and bipolar depression.[167,168] However, clinically, lithium is disadvantaged in the treatment of bipolar depression because of a delay in efficacy of 6–8 weeks compared with 6–10 days in acute mania.[167]

Maintenance Therapy

The potential delay in the antidepressant effect of lithium is of little consequence as regards maintenance therapy, where empirically lithium has been shown to have prophylactic properties lasting for many years. A systematic review of RCTs has demonstrated clearly the efficacy of lithium in bipolar disorder,[169] and two recent meta-analyses of lithium treatment have reconfirmed its maintenance efficacy, particularly in relation to manic relapse in bipolar disorder.[170,171]

Furthermore, there is increasing evidence that long-term lithium treatment reduces the risk of suicide and suicidal behaviour in both recurrent depression and bipolar disorder.[172,173] Balanced against this, however, is the diminished likelihood of treatment adherence, given its adverse effect burden, and the increased risk of relapse on rapid discontinuation.[174] Interestingly, lithium responders appear to have 'classic bipolar disorder' with an episodic illness that is predominantly depressive and includes periods of complete symptom-free remission.[161,162]

4.1.2 Anticonvulsants

Valproate

Acute mania: in two large RCTs of acute mania, valproate has demonstrated superior efficacy to

placebo.[175,176] In the first of these trials, Bowden et al.[175] reported response rates for valproate (48%) that were superior to placebo (25%) and comparable to lithium (49%), and these findings led to the approval of valproate by the US FDA for treating acute manic episodes in patients with bipolar disorder. The efficacy of valproate against placebo is further supported in a smaller trial of 36 patients who were non-responsive to, or intolerant of, lithium.[177] Valproate was comparable to lithium in a 12-week RCT of acute mania[178] and superior to lithium in a double-blind trial of patients with mixed episodes.[69]

The onset of antimanic activity in these studies generally occurred within several days to 2 weeks of achieving a serum valproate concentration of ≥50 mg/L. Valproate loading is thought to accelerate the onset of its treatment effect and in a double-blind RCT, initial high oral doses of valproate of 30 mg/kg/day for the first 2 days, and then 20 mg/kg/day for days 3–10, compared with control groups of valproate non-loading or lithium, led to a more rapid achievement of therapeutic serum concentrations with no increase in adverse events.[179] A more rapid onset of an antimanic effect with dose loading has also been reported in a small double-blind pilot study with an oral loading of 20 mg/kg/day[180] and an earlier open-label trial that also used 20 mg/kg/day.[181]

Bipolar depression: evidence for an antidepressant effect of valproate in bipolar depression is relatively limited;[182] however, based on a number of recent trials, valproate is fast accumulating evidence as a potential treatment for bipolar depression. Two recent pilot RCTs report superiority over placebo,[183,184] and an earlier open-label trial of medication-naive patients with bipolar II depression observed a good response to valproate.[185] A comparison of response rates in uncontrolled trials suggests that valproate may not be as effective in treating bipolar depressive episodes when compared with manic episodes[186] and, therefore, more data are needed.

Maintenance: despite its widespread use, there is surprisingly little evidence to support the efficacy of valproate as a maintenance treatment for bipolar disorder, especially in the prevention of manic episodes. A Cochrane review identified only one RCT eligible for inclusion and found that the findings from this study were equivocal.[187] This trial, conducted by Bowden et al.,[188] reported no differences between valproate, lithium or placebo in time to next mood episode (manic or depressive episode), although valproate was superior to lithium in some secondary measures, including length of successful prophylaxis and less deterioration on depressive and global assessment scales. However, the design of this study was not enriched and, thus, it is harder to demonstrate clinical benefit and it is likely to compare less favourably with trials of other medications that use enriched designs. A *post hoc* analysis of these data, which employed an enriched design and the findings of which are therefore perhaps more comparable to trials of lamotrigine and the newer atypical agents, found that valproate was superior to lithium in a number of measures related to depressive symptoms, particularly in those patients who had responded to valproate during an acute manic phase or those with a more severe course of illness.[189]

Subsequent to this Cochrane review, two randomized trials including valproate as maintenance treatment have been published. In one trial of 60 patients, valproate was found to be comparable to lithium in the maintenance treatment of rapid-cycling bipolar disorder over 20 months.[76] However, there were mixed results in another trial that compared valproate with olanzapine.[190] In this study, valproate was not as effective as olanzapine in overall improvement of manic symptoms and the median time to achieve symptomatic remission; however, the two groups did not statistically differ in rates of achieving remission from mania or relapse to any mood episode.[190]

Lamotrigine

Mania: there is a single lithium-comparator trial of lamotrigine in mania;[191] however, there are no randomized placebo-controlled studies indicating that lamotrigine has an effect in the treatment of mania,[192,193] and a review of available data found it to be ineffective in the treatment of acute mania.[194] Its efficacy in bipolar disorder may be thought of as 'stabilizing mood

from below' in that it has a maximum impact on depressive symptoms.

Bipolar depression: while lamotrigine has been shown to be superior to placebo in two RCTs of bipolar depression,[192,195] recent findings have questioned its efficacy. In addition to their original trial, Calabrese et al.[196] reported on a further four RCTs and found that lamotrigine monotherapy did not differ from placebo in the acute treatment of bipolar depression. These studies reported a large placebo response in four of the five trials, which may have contributed to the lack of significant differences between lamotrigine and placebo. Therefore, to better understand these findings, further trials with an active comparator are warranted.[196] It is noteworthy that a recent meta-analysis of lamotrigine bipolar depression studies found a 'modest' effect size in favour of lamotrigine over placebo,[197] although the difference in a clinical sense is minimal, translating to approximately just one point on the depression outcome measure.[197]

In addition, the adjunctive use of lamotrigine has been supported by a randomized, double-blind, placebo-controlled trial.[198] In light of these findings, the efficacy of lamotrigine monotherapy remains to be established, although there is some evidence to support its use.

Maintenance: in maintenance therapy, lamotrigine has been found to be more effective than placebo in prolonging time to recurrence; however, it is not more effective in reducing the number of recurrences.[199] Specifically, it is more effective in prolonging time to intervention for a depressive episode. The two 18-month, double-blind studies that compared lamotrigine, lithium and placebo led to the FDA approval of lamotrigine as a maintenance treatment for bipolar I disorder.[191,136] The results of these trials support the use of both lamotrigine and lithium in maintenance treatment of bipolar disorder, but at the same time highlight their different therapeutic effects. Although both have a role in the prevention of bipolar relapses, lamotrigine appears to possess greater efficacy with regards to depressive recurrences than lithium, although it is somewhat favoured by an enriched study design.

Carbamazepine

Acute mania: not surprisingly, many of the early reports on carbamazepine involve small trial numbers and are confounded by the co-administration of lithium or typical antipsychotics.[137] However, a review of five double-blind, controlled trials by McElroy and Keck[200] suggests that carbamazepine potentially has comparable efficacy to lithium in the treatment of acute mania and the typical time for carbamazepine response is between 1 and 2 weeks. While an RCT of 30 inpatients found that carbamazepine was not as effective as valproate,[201] an extended-release preparation of carbamazepine has recently been studied as monotherapy in the treatment of acute bipolar mania using a 3-week, placebo-controlled, double-blind design. An analysis of the data from 427 subjects in the intent-to-treat population from two studies reports response rates of 42% and 61% for carbamazepine-treated subjects compared with response rates of 22% and 29% in placebo groups, respectively.[71,202] Furthermore, comparator studies have shown carbamazepine to be as effective as lithium.[203] Therefore, in practice it is still used to treat patients with bipolar disorder but predominantly those who have not responded to other agents.

Bipolar depression: carbamazepine has been shown to be superior to placebo in two small double-blind RCTs;[204,205] however, there are no adequately controlled trials of carbamazepine in bipolar depression to warrant a monotherapy indication for this pole of the illness.[206]

Maintenance: there are little data to support carbamazepine as a maintenance treatment and in the limited trials that have been conducted, carbamazepine compares unfavourably with lithium.[207,208] However, there is some evidence that carbamazepine may be more effective than lithium in patients with non-classical bipolar disorder, including patients with bipolar II disorder, bipolar not otherwise specified, and those patients with non-classical symptoms such as mood-incongruent delusions or co-morbidities.[209] More recently, extended-release carbamazepine, which is better tolerated, has been studied as a maintenance therapy in an open-label extension phase of a

double-blind acute trial of patients with mixed or manic bipolar disorder and the evidence supports its use in prophylaxis.[210]

Oxcarbazepine

Oxcarbazepine is an anticonvulsant similar to carbamazepine. Recent pilot trials provide some promise for oxcarbazepine as adjunctive treatment in acute and maintenance phases of bipolar disorder.[211,212] However, larger double-blind, randomized, controlled studies are still needed. Of note, neither carbamazepine nor oxcarbazepine currently carry any FDA indications for the treatment of bipolar disorder.

Other Anticonvulsants

Acute mania: in the treatment of acute mania, gabapentin has not been found to be any more effective than placebo either as monotherapy[192] or as adjunctive treatment with lithium or valproate.[213] Topiramate has failed to demonstrate sufficient efficacy in the treatment of acute mania in four randomized placebo-controlled and comparator trials.[214,215] However, as with gabapentin, topiramate has been effective in the treatment of bipolar disorder co-morbidities[216] and, as such, some speculation as to its usefulness remains. Phenytoin, adjunctive to haloperidol, significantly reduced symptoms of acute mania in a small, 5-week, placebo-controlled trial.[217]

Bipolar depression: in the treatment of bipolar depression, there are no large-scale trials or RCTs that support the use of gabapentin, topiramate or phenytoin, and gabapentin produced only modest effects in an open-label trial.[218]

Maintenance: in the maintenance phase of bipolar disorder, adjunctive gabapentin provided additional prophylactic benefit in one small RCT.[219] There is no evidence to support topiramate having a prophylactic action. Phenytoin has shown promise in a small, 6-month, double-blind, crossover study as an adjunct to usual treatment.[220]

4.1.3 Antipsychotics

Antipsychotics have long been used in the treatment of mania but tolerability issues, in particular extrapyramidal side effects (EPS) with long-term use, have precluded their use in bipolar disorder prophylaxis. However, with the development of atypical antipsychotics, their use has been the focus of renewed interest. Indeed, the majority of bipolar disorder treatment trials in recent years have investigated the efficacy of atypical antipsychotic agents.

Olanzapine

Acute mania: olanzapine has demonstrated its superiority over placebo in two RCTs.[221,222] In these two studies, a drop of 50% or more in the total Young Mania Rating Scale score was reported for 48.6% and 64.8% of patients treated with olanzapine, but only 24.2% and 42.9% of patients treated with placebo in the first and second study, respectively. Furthermore, *post hoc* analyses of the pooled data showed that olanzapine was effective in the treatment of acute mania irrespective of patient characteristics, psychosis, and mixed or pure status.[223] Compared with other medications, olanzapine has been shown to be at least comparable with valproate[190,224] and lithium,[225,226] and when used as an adjunct to lithium or valproate is superior to monotherapy with either agent.[227] Thus, olanzapine has FDA approval for the treatment of mania in conjunction with lithium or valproate. Interestingly, a recent 6-week, double-blind, randomized trial failed to find any additional benefit when olanzapine was added to carbamazepine (63.8% response rate) compared with carbamazepine monotherapy (66.1% response rate).[228]

Bipolar depression: olanzapine and OFC were both found to be superior to placebo in an 8-week RCT of 833 patients with bipolar depression. However, on the primary outcome measure, the benefits of olanzapine monotherapy were primarily seen with neurovegetative symptoms, sleep and appetite, and its translation into clinical benefit is uncertain with an overall therapeutic effect size of just 0.32. In contrast, OFC did demonstrate significant improvement on core mood items and was also superior to olanzapine monotherapy in the acute treatment of bipolar depression (effect size 0.68).[229,230] In addition, an RCT has further demonstrated the superiority of OFC over lamotrigine monotherapy in the treatment of bipolar depression[231] and the proprietary OFC is

FDA approved for the treatment of bipolar depression.[231] However, the combination is also associated with an increased rate of adverse effects, including weight gain, and raised triglycerides and cholesterol. Importantly, it is also difficult to directly compare the efficacy of OFC with antidepressant treatment as neither trial included an active fluoxetine arm.

Maintenance: in maintenance therapy, olanzapine has a strong evidence base with four RCTs having investigated its efficacy.[190,232-234] In one trial, patients treated with olanzapine monotherapy had a significantly longer duration until the next mood episode (median 174 days) compared with placebo (median 22 days), and the relapse rates were also significantly lower in the olanzapine group (47%) when compared with placebo (80%).[232] Furthermore, olanzapine was significantly more effective than lithium in preventing the recurrence of manic or mixed episodes, whereas both agents were comparable in preventing the recurrence of depression.[233] Compared with valproate, there were no significant differences in relapse rates[190] and, as an adjunctive treatment, olanzapine added to lithium or valproate improved time to symptomatic relapse but not syndromic relapse compared with lithium or valproate monotherapy.[234] However, as discussed earlier (see section 4.1), maintenance studies in bipolar disorder that adopt an enriched design are limited by the level of clear separation of prophylaxis from relapse prevention. Furthermore, in a clinical context it is important to acknowledge that most maintenance studies fall significantly short of reality where prophylaxis for several years is needed.

Quetiapine

Acute mania: quetiapine has been shown to be efficacious in the treatment of mania in two placebo-controlled trials,[235,236] to be of comparable efficacy to lithium[237] and, in adolescents, comparable to valproate.[238] It has also demonstrated its efficacy when used as an adjunctive treatment to lithium or valproate.[74,239] There are also emerging data to support the efficacy of quetiapine in its extended-release form, quetiapine XR, in acute mania.[240] Quetiapine is FDA approved for the treatment of mania in conjunction with lithium or valproate.

Bipolar depression: adding support to earlier open-label studies and preliminary trials,[241,242] the BOLDER studies[50,51] and EMBOLDEN data[52,53] support the efficacy of quetiapine monotherapy in the acute treatment of bipolar I and II depression. Furthermore, pooled data from the BOLDER trials targeting just patients with bipolar I depression have shown that quetiapine monotherapy is superior to placebo.[243] In light of these data, a number of guidelines have positioned quetiapine as first-line therapy.[244-246] Moreover, it appears that quetiapine XR may also be effective in bipolar depression, with abstract data reporting superior efficacy over placebo in 270 patients with bipolar I and II depression.

Maintenance: when compared with placebo or when added to lithium or valproate, quetiapine appears to confer additional benefit and increase the time to recurrence of any event (mania, depression) irrespective of the polarity of the index episode.[247-249] Furthermore, preliminary evidence for monotherapy maintenance for up to 2 years suggests that quetiapine may be as effective as lithium in the prevention of relapse into any mood episode,[250] although it is noteworthy that the design of the study favours quetiapine. Therefore, it is likely that quetiapine will emerge as an alternative to olanzapine with at least equivalent efficacy in bipolar maintenance therapy.

Risperidone

Acute mania: risperidone was the first of the atypicals to demonstrate efficacy in bipolar disorder.[251,252] It is established as an effective treatment for mania and has demonstrated superiority to placebo in two trials[253,254] with comparable efficacy to lithium in another.[251] As an adjunctive treatment, risperidone has been shown to be effective in conjunction with lithium or valproate in one RCT[74] but not in another, in which risperidone was added to either lithium, valproate or carbamazepine.[255] However, the plasma levels of risperidone may have been affected by carbamazepine. In the US, risperidone

is FDA approved for the treatment of mania in conjunction with lithium or valproate.

Bipolar depression: limited data exist for the use of risperidone in bipolar depression; however, those which are available lend support to its potential antidepressant effect when used as an adjunctive treatment. An open-label trial in which risperidone was added to usual treatment for depression in bipolar II patients reported clinical improvement.[256] An RCT of 30 patients with bipolar I or II depression reported modest but comparable improvements in depressive symptoms when risperidone, paroxetine or a combination of risperidone and paroxetine were added to existing treatment.[257] Conversely, a randomized open-label risperidone augmentation trial for treatment-resistant bipolar depression reported a 5% rate of sustained recovery over 8 weeks. Remarkably, this recovery rate did not differ statistically from either lamotrigine (24%) or inositol (17%), indicating the limited statistical power of this study.[258]

Maintenance: there are no RCTs of risperidone as a maintenance treatment in bipolar disorder. However, open-label data over periods of 3 and 6 months suggest that risperidone adjunctive to valproate or lithium improves both manic and depressive symptomatology.[255,259] Abstract data have been presented supporting the efficacy of long-acting risperidone injection as an adjunctive maintenance treatment in bipolar disorder.[260]

Aripiprazole

Acute mania: three RCTs provide support for the acute antimanic properties of aripiprazole when compared with placebo with a significant reduction in manic symptoms in each of these 3-week studies.[73,261,262] In comparator studies, aripiprazole has been shown to be similar to both lithium[261] and haloperidol.[263]

Bipolar depression: two recent aripiprazole monotherapy RCTs assessing the treatment of bipolar depression failed to report any benefit over placebo at the 8-week endpoint, although the groups separated at 6 weeks and at other timepoints in the study.[264] However, a small open-label trial that examined the addition of aripiprazole to existing treatment with an antidepressant and/or valproate, lithium or carbamazepine has reported a significant antidepressant effect.[265]

Maintenance: in a 26-week, randomized, double-blind, placebo-controlled trial in bipolar patients who had experienced a recent manic or mixed episode, aripiprazole was shown to be an effective maintenance treatment with significantly fewer relapses (25%) than placebo (43%).[266] In a further 74-week extension phase of this study, time to relapse was superior in the aripiprazole group for manic episodes but no difference was detected for depressive episodes.[267]

Ziprasidone

Ziprasidone has demonstrated dose-related antimanic efficacy over placebo in two RCTs.[268,269] In each of these 3-week monotherapy trials, the mean dose of ziprasidone was 120–130 mg/day. Of note, ziprasidone failed to show superiority to placebo as an adjunct to lithium,[270] but in another trial, was superior to placebo and comparable to haloperidol.[271] There are limited data for ziprasidone as an antidepressant and as maintenance treatment. However, available open-label data suggest that ziprasidone may be useful as monotherapy or in combination with lithium for bipolar disorder prophylaxis.[272]

Other Atypical Antipsychotics

Clozapine has useful antimanic and prophylactic properties in the treatment of mania. However, remarkably there have been no documented double-blind clinical trials of clozapine in the treatment of bipolar disorder. In the treatment of refractory bipolar disorder, clozapine has been used at doses similar to those used to treat schizophrenia with some success and in one randomized trial, adjunctive clozapine significantly improved symptomatology in patients with refractory mania.[273] As a maintenance treatment option, an open-label trial and a retrospective analysis of case reports of bipolar patients resistant to conventional treatments have reported that the addition of clozapine significantly reduces symptoms, and also the number and duration of hospitalizations.[274,275] Clozapine is generally reserved for treatment refractory bipolar disorder.

Amisulpride has been studied in one 6-week open-label trial of 20 patients with acute mania.[276] Significant improvements were noted with respect to symptomatology as well as on scales specific to both mania and depression, suggesting that further trials are warranted.

There are abstract data showing that asenapine, a new atypical antipsychotic, added to lithium or valproate was superior to placebo at reducing manic symptoms in an RCT of 318 patients.[277] Other atypical antipsychotics currently under investigation as antimanic agents include paliperidone and bifeprunox.

Typical Antipsychotics

As noted earlier, typical antipsychotics have been largely supplanted by the atypicals because of greater tolerability; however, typical antipsychotics are still used in the treatment of acute mania and, of these, haloperidol has established efficacy both against placebo and active comparators, such as quetiapine.[236,278] However, haloperidol is seldom used as a first-line treatment option because of its greater potential for adverse effects compared with other antimanic agents. Furthermore, there is evidence to suggest patients with bipolar disorder may be more susceptible than patients with schizophrenia to antipsychotic-induced EPS.[279] However, in patients who do not respond to other first-line agents, haloperidol is an effective alternative. Chlorpromazine has also been shown to be superior to placebo in the treatment of mania,[280] and both chlorpromazine and haloperidol have been shown to have comparable antimanic efficacy to lithium.[281,282]

4.1.4 Antidepressants

The use of antidepressants in the treatment of bipolar depression has been extrapolated from their use in the treatment of unipolar depression, in much the same way as anticonvulsants were transposed from the treatment of epilepsy. Indeed, the research base for antidepressant use in bipolar disorder has been drawn largely from studies of populations with unipolar depression and there has been limited systematic research in bipolar depression.[7,283] Interestingly, the research that has been conducted in populations with bipolar depression has yielded equivocal findings and the role of antidepressants remains unclear.[40,60,283,284]

Two decades ago, fluoxetine was shown to be superior to placebo in a double-blind, placebo-controlled trial of bipolar depression[285] and more recently, in a pilot RCT of bipolar I and II depression, it has been shown to have efficacy either alone or in combination with olanzapine.[286]

Paroxetine as an add-on to either lithium or valproate was comparable to a combination of lithium and valproate in a double-blind study in bipolar I or II disorder,[287] but of note, the number of withdrawals were greater in the group treated with a combination of lithium and valproate. Furthermore, in a placebo-controlled trial of bipolar I depression, paroxetine or imipramine added to ongoing lithium treatment were only effective in those patients with serum lithium levels <0.8 mmol/L.[288]

Interestingly, in the treatment of bipolar depression, the response to venlafaxine (48%) did not statistically differ to paroxetine (43%) when it was prescribed as an adjunct to mood stabilizers in a non-placebo-controlled trial.[289] Furthermore, as adjunctive therapy, venlafaxine is no better than bupropion or sertraline and adjunctive bupropion is no better than desipramine.[290]

Three important studies conducted recently have failed to show any significant benefits of adjunctive antidepressant treatment in bipolar depression. The first study, from the Stanley Foundation Bipolar Network, involved augmentation of lithium or an anticonvulsant with sertraline, bupropion or venlafaxine. There was no significant difference in response when an antidepressant was added to ongoing treatment.[65] The second study, the STEP-BD study,[60] added antidepressants (paroxetine or bupropion) or placebo to lithium or anticonvulsant treatment in patients with bipolar I and II depression. Remarkably, the response to the addition of an antidepressant was less (23.5%) than that observed with the addition of placebo (27.3%). The EMBOLDEN II study, which had a paroxetine and placebo arm, failed to show differences between the two.[53] The failure of antidepressants to demonstrate efficacy in any of these trials, which

are the largest and most methodologically rigorous, is of substantial concern given the paucity of options and the predominant burden of bipolar depression.

Traditionally, antidepressants have been associated with treatment-emergent affective switching (TEAS) [the development of hypomania/mania] that occurs through a hitherto unknown mechanism. In this regard, tricyclic antidepressants appear to carry the highest risk (7–11%) of TEAS compared with SRIs (0–4%),[283,288,290,291] but venlafaxine is also associated with an increased risk of TEAS (13–15%).[289,292] However, the overall risk may be no greater than placebo when antidepressants are used adjunctively in combination with lithium or an anticonvulsant.[60,293] Therefore, it is generally recommended that antidepressant medications are coadministered with a mood stabilizer.[165,245,294,295] In addition to the potential for TEAS, tricyclic antidepressants may also trigger longer-term cycle acceleration in bipolar patients. Prospective longitudinal observations over a 5-year period in one small placebo-controlled trial identified a link between tricyclic antidepressant use and onset of rapid cycling.[296] This is further supported by the initial success achieved in the STEP-BD trials where, in rapid-cycling patients, antidepressant use is gradually tapered in favour of agents such as lithium, lamotrigine, olanzapine, aripiprazole or valproate.[33]

4.1.5 Combinations

Data on combination trials remain limited but are increasing and combinations are frequently used clinically, particularly when there has been an inadequate response to monotherapy (table III).

In acute mania, recent studies including a meta-analysis of eight RCTs have shown superior efficacy when an atypical antipsychotic is added to lithium or valproate compared with lithium or valproate monotherapy.[297,298] In bipolar depression, OFC has demonstrated superior efficacy compared with both placebo and olanzapine monotherapy.[229] Other combinations with RCT evidence to support their use in bipolar depression include lamotrigine added to lithium[299] and lithium combined with valproate.[287] There are emerging data from two RCTS currently published in abstract form supporting the efficacy of quetiapine added to lithium or valproate during maintenance.[247,300,301]

4.1.6 Novel Pharmacological Agents

In recent years, a number of promising novel pharmacological agents have emerged and have undergone initial trials in bipolar disorder. The mechanisms of action of these agents are diverse and in some cases unclear. Examples include *N*-acetyl cysteine,[302] omega-3 fatty acids,[303] tamoxifen,[304,305] asenapine,[277] antiglucocorticoids,[306] celecoxib,[307] modafinil[57] and pramipexole.[56] In all cases, further trials are needed before specific recommendations can be made.

4.1.7 Dosing and Adverse Effect Considerations

Lithium

Lithium is generally well tolerated but can cause both short- and long-term adverse effects that can affect compliance. Dosing can be monitored by measuring serum levels, and therapeutic levels for use in bipolar disorder have been identified.

Common adverse effects of lithium include polyuria, nausea, diarrhoea, weight gain and tremor. These can usually be managed by modifying dosage and reducing serum levels. More potentially severe adverse effects include thyroid and renal dysfunction. Hypothyroidism occurs in 1–30% of patients and, less commonly, patients can develop euthyroid goitre. Both are amenable to treatment with thyroxine.[308]

Anticonvulsants

Common dose-related adverse effects of anticonvulsants include CNS disturbances such as dizziness and headache. Rare but potentially serious adverse effects include severe skin rashes (e.g. Stevens-Johnson syndrome), abnormalities of blood or platelet counts (agranulocytosis, aplastic anaemia), as well as abnormalities of liver function. Hepatic and haematological function should therefore be monitored regularly.[309]

While the link between PCOS and valproate has not been clearly determined, there is sufficient evidence to recommend routine monitoring for reproductive-endocrine abnormalities (menstrual cycles, bodyweight and symptoms of

hyperandrogenism) in women with child-bearing potential who are taking valproate.[109]

Unlike lithium, there are no therapeutic serum levels for the use of anticonvulsants in bipolar disorder; however, as a guide, the epileptic therapeutic range for each medication is often applied. However, some anticonvulsants interact with concomitant medications; for example, valproate inhibits the metabolism of lamotrigine and, if administered together, the dose of lamotrigine should be halved. In addition, carbamazepine impacts on the cytochrome P450 system and can affect drugs also metabolized by this system including other anticonvulsants, risperidone, corticosteroids, warfarin, haloperidol and antidepressants.[310] The safety and tolerability of carbamazepine limit its utility as a first-line agent and, in practice, this is the main reason for its discontinuation.[137]

Antipsychotics

While the type and likelihood of adverse effects varies with the specific drug, atypical antipsychotics in general are associated with metabolic syndrome, EPS, anticholinergic reactions, sedation, hypersalivation, lowered seizure threshold, raised prolactin and sexual dysfunction, prolonged corrected QT (QTc) interval and orthostatic hypotension. Compared with conventional antipsychotics, the atypical antipsychotics appear to have a much lower risk for tardive dyskinesia but do confer additional risks.[311]

Olanzapine and clozapine are associated with a greater risk of metabolic effects including weight gain, anticholinergic effects and sedation than other atypicals. Quetiapine is moderately related to increased metabolic risk and sedation; however, of the atypicals, it is least likely to produce EPS. Risperidone and aripiprazole are more likely to result in dose-related EPS and risperidone is also more likely to be associated with raised prolactin and, as a consequence, reduction in bone mineral density[312] and sexual dysfunction. Amongst the atypical antipsychotics, orthostatic hypotension is the most commonly reported cardiovascular adverse event.[313] With the exception of clozapine, atypical antipsychotics do not require any therapeutic monitoring of serum levels. Clozapine requires close monitoring due to potentially fatal adverse effects.[314] Furthermore, because most atypical antipsychotics, especially olanzapine and clozapine, are known to cause significant weight gain, it is considered good practice to routinely monitor for symptoms of metabolic syndrome.[315] Comprehensive safe monitoring guidelines are available.[316]

Conventional antipsychotics are more likely than atypical antipsychotics to be associated with EPS, anticholinergic effects, raised prolactin and sexual dysfunction, increased risk of prolonged QTc interval and tardive dyskinesia. High prevalence rates of tardive dyskinesia have been reported in patients with mood disorders,[317] with one study that compared psychiatric diagnoses noting almost double the prevalence of tardive dyskinesia in bipolar disorder compared with schizophrenia.[318] Where possible, the long-term use of atypical antipsychotics should generally be avoided in the treatment of bipolar disorder.

Antidepressants

Compared with other antidepressants, SRIs tend to be safer and better tolerated by bipolar patients, with a more favourable safety and adverse effect profile, even at high doses.[319] However, adverse effects are still common and include gastrointestinal disturbances (nausea, vomiting, diarrhoea), sexual dysfunction and with some antidepressants, sedation and fatigue. However, many of the adverse effects of SRIs tend to be transient and cease within a few days or weeks after commencing treatment.[320]

4.2 Psychological Interventions

There is good evidence to suggest that psychological interventions are effective in their own right and provide additional benefit to pharmacotherapy in bipolar disorder. A recent review of psychological treatments in bipolar disorder suggested that treatments emphasizing medication adherence and early recognition of mood symptoms may have a stronger effect on mania, whereas treatments that target cognitive and interpersonal coping strategies appear to have a greater impact on depression.[321] A Cochrane

review identified six, high-quality RCTs and concluded that interventions targeted at improving the recognition of EWS and self-management of manic and depressive symptoms improved the time to recurrence, reduced hospitalization rates and improved functioning in people with bipolar disorder.[67] Furthermore, a meta-analysis of psychosocial interventions for relapse prevention in bipolar disorder found that CBT, group psychoeducation and, possibly FFT, are likely to be beneficial adjunctive treatments in the maintenance phase of bipolar disorder.[322] The psychological treatments used to manage bipolar disorder are quite diverse and include a number of different strategies such as CBT, psychoeducational interventions and FFT.

4.2.1 Psychoeducation

It is recommended that psychoeducation be part of routine interventions in bipolar disorder.[323] RCTs have demonstrated that psychoeducation, adjunctive to pharmacotherapy, can significantly delay time to recurrence over a 2-year follow-up and improve functioning.[324-326] Family involvement in psychoeducation is also supported by a recent RCT where there was a reduction in both the number of recurrent episodes and time to recurrence for the group of bipolar patients whose carers were involved in a psychoeducation programme.[327]

4.2.2 Cognitive Behavioural Therapy

CBT, originally developed as a treatment for unipolar depression,[328] has been adapted for bipolar disorder.[329,330] In bipolar disorder, CBT aims to assist the patient to recognize illness onset and achieve early intervention, to manage behaviours that occur as a result of the illness, and to address associated thoughts and behaviours.

Two RCTs have shown CBT, administered adjunctive to usual treatment over 6 months, to be effective at reducing the frequency of episodes and improving social functioning.[331,332] Similarly, a pilot trial of 6 months' adjunctive CBT for 42 patients with bipolar I or II disorder reported significant improvements, compared with waiting list controls, in depressive symptoms and global functioning.[333]

Follow-up data suggest that CBT may have particular benefit at sustaining treatment gains.[333-336] For example, in a 2-year follow-up, Lam et al.[335] reported significantly lower relapse rates (63.8%) when compared with control conditions (84.3%), with most benefit during the first year following treatment. At 18 months' follow-up, Scott et al.,[333] reported a 60% reduction in relapse rates in those who had received CBT.

However, the ongoing protective effect of CBT has not been reported universally. In a large RCT where patients with severe and recurrent bipolar disorder received 22 sessions of CBT adjunctive to usual treatment, over half of patients had relapsed within 18 months of completing treatment, and there were no differences between the treatment and control groups.[45] However, a *post hoc* analysis revealed a significant difference with regard to treatment response and the number of previous episodes: CBT was significantly more effective at reducing relapse rates in those patients with fewer than 12 prior episodes (41%) compared with patients with more than 12 prior episodes (81%).[45] These findings suggest that psychological interventions in bipolar disorder, specifically CBT, may be most effective when instituted early in the course of the illness.

While most studies of CBT in bipolar disorder typically target patients in the maintenance phase, there is some indication that these therapies may also be beneficial during the depressed phase.[337] Data from the STEP-BD trials, the largest study to date of adjunctive psychosocial interventions in bipolar depression, have reported that psychosocial interventions, including CBT, IPSRT and FFT, significantly improved depressive symptoms, increased the likelihood of recovery[338] and resulted in functional improvement, particularly in life satisfaction and relationship functioning.[43]

4.2.3 Family-Focused Therapy

Developed by Miklowitz and Goldstein,[339] FFT includes a combination of psychoeducation and skills-based training provided to the patient and family over a 9-month period following an episode of bipolar illness. In FFT, therapists work to identify difficulties and conflicts within the family that

may contribute to patient and family stress, and then help the involved family members to find ways to resolve those difficulties and conflicts.

RCTs of FFT adjunctive to pharmacological treatment have shown positive benefits, including reductions in mood disorder symptoms, improved adherence to medication and fewer relapses over follow-up periods of up to 2 years, when compared with both individual-oriented therapies[340] and less intensive crisis management and basic psychoeducation.[341,342]

FFT was also part of the STEP-BD trial that examined adjunctive benefits of psychosocial interventions compared with antidepressants and this trial reported that psychosocial interventions as a whole enhance the likelihood of recovery over 9 months.[338]

However, the benefits of this targeted intervention may not necessarily be extrapolated to family therapy more generally. A Cochrane review of RCTs of family therapy interventions, encompassing a broader range of therapies not exclusive to FFT, was unable to find sufficient evidence to make any clear conclusions about the added benefit of family therapy in the treatment of bipolar disorder.[343] It had been suggested that family-based interventions benefit families with high levels of impairment more so than those with low levels of impairment.[344]

4.2.4 Interpersonal and Social Rhythm Therapy

IPSRT is an adaptation of interpersonal psychotherapy in accordance with the social zeitgeber hypotheses,[345] which argue that the disruption of tasks that would normally set the biological clock, such as sleep and daily routines, causes destabilization of circadian rhythms, and this can trigger affective episodes in mood disorders.[345] Therefore, the treatment focuses on the links between mood symptoms and quality of social relationships and social roles, the importance of maintaining regularity in daily routines, and the identification and management of potential precipitants of rhythm disruption.

A 2-year non-blinded RCT compared the addition of either IPSRT or intensive clinical management with usual pharmacological treatment in a group of patients with bipolar I disorder. Patients entered the study in any phase of illness and, while there were no initial differences in time to recovery, the study reported that over a 2-year period, patients treated with IPSRT during the acute phase had longer survival times until recurrence of an affective episode, irrespective of the treatment type received by patients during the maintenance phase.[346,347] Furthermore, data from the STEP-BD trials found that intensive psychosocial interventions, including IPSRT, improved depressive symptoms, increased the likelihood of recovery and improved levels of functioning.[43,338]

4.2.5 Mindfulness-Based Cognitive Therapy

Developed by Segal et al.,[348] MBCT incorporates elements of Beck's cognitive therapy[328] and Kabat-Zinn's mindfulness-based stress reduction.[349] MBCT differs from traditional CBT in that it does not focus on trying to change the content of thoughts, rather, it emphasizes the process of attending to thoughts and feelings and experiencing these without judgment.

MBCT has shown promise in the treatment of recurrent unipolar depression[350] and is now being evaluated in bipolar patients in a pilot RCT.[94] The study targets inter-episode symptoms of anxiety and depression in patients with remitted bipolar disorder with symptoms of suicidal ideation or behaviour, and has reported modest improvements.[94] It has been suggested that where CBT may be better applied to those earlier in the course of their bipolar illness,[45] MBCT is perhaps better suited to those with a more recurrent pattern of illness.

4.3 Physical Treatments

4.3.1 Electroconvulsive Therapy

While there are limited controlled studies of ECT in bipolar disorder, it is widely considered to be a safe and effective treatment, particularly when the symptoms are severe or the patient poses a substantial risk to themselves or others.[351]

ECT has been used for the treatment of mania and in one RCT, it has been shown to be demonstrably better than lithium.[352] A review of non-controlled trials of ECT in mania concluded that ECT is also better than a combination of lithium and haloperidol, and that it is an effective

and safe treatment that achieves remission or marked clinical improvement in 80% of patients.[353] It is of note that this is not attained with sham ECT,[354] but with the exception of case reports or naturalistic studies,[355,356] few studies have taken the investigation of ECT further with regard to the treatment of mania.

The antidepressant effects of ECT have been researched mainly in unipolar depression. Comparisons of open-label trials and retrospective studies between bipolar depression and unipolar depression have demonstrated comparable efficacy of ECT.[357,358] In the 1990s, a review of bipolar depression identified nine trials relating to ECT, including three controlled trials, and concluded that ECT was superior to placebo and at least as effective as, and in most studies more effective than, antidepressants.[359] Furthermore, the speed of response to ECT has been found to be quicker than to antidepressant therapy in bipolar depression,[360] and a recent retrospective chart review reported superior efficacy of ECT over venlafaxine in treatment-refractory bipolar depression.[361] However, there is a suggestion that the use of ECT in bipolar disorder may not be as efficacious as in unipolar depression.[362] ECT is nevertheless considered an effective treatment option for severe bipolar depression, particularly if psychotic features are present.[244] Research into maintenance treatment using ECT consists largely of case series, naturalistic studies and retrospective reports. Hence, the available data are methodologically flawed but do provide empirical support for the use of ECT in the long-term maintenance of treatment-resistant bipolar disorder.[363]

Dosing and Adverse Effects Considerations

Seizure duration is monitored during ECT using either the blood pressure cuff method or EEG. On average, 1.5 fewer treatment sessions are required in bipolar disorder compared with unipolar depression. In particular, around 42% of patients with bipolar depression required five or fewer treatments and <6% required ten or more treatments.[364] In both unipolar and bipolar depression, right unilateral high-dose ECT has similar efficacy to bilateral ECT but causes fewer cognitive adverse effects.[365] However, relapse is common because of the inherent nature of depressive disorders. Furthermore, bifrontal ECT that uses a lower electrical dose to achieve a seizure has fewer cognitive adverse effects but achieves similar efficacy to bitemporal ECT.[366]

The risks and adverse effects associated with ECT occur either because of the ECT itself or as a result of anaesthesia. Symptoms of nausea, headaches and muscle aches are usually short-lived, and can be managed with antiemetics and analgesics.[367] Cognitive impairment post-ECT is an ongoing source of controversy with short-term anterograde amnesia common during ECT. The latter tends to resolve within a matter of weeks after the completion of treatment;[368] however, retrograde amnesia, where memories prior to ECT are affected, may not fully resolve.[368] The presence of cognitive impairment prior to ECT has been linked to retrograde amnesia and post-ECT confusion,[369] although the definitive effect of ECT remains unclear. ECT is not recommended with co-existing unstable cardiovascular illness or increased intracranial pressure;[368] however, it is generally regarded to be a relatively safe treatment.[370]

4.3.2 Other Physical Treatments

In addition to ECT, other physical treatments that are currently being investigated in the treatment of bipolar disorder include vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy and deep brain stimulation.[371-373] Most of the research has been focused on unipolar depression and, in this regard, rTMS is not as effective as ECT.[374] However, some studies have specifically investigated bipolar disorder;[375] for instance, rTMS has been shown to be effective in small RCTs and case series,[376,377] but as with antidepressants, it may also lead to treatment emergent mania.[378] A trial of VNS found comparable efficacy in both unipolar and bipolar depressed patients,[379] but further research is needed.

4.4 Lifestyle Interventions

Lifestyle interventions together with psychological and pharmacological therapy contribute to optimal treatment outcomes. The quality of social supports and networks predicts outcome,

and it is helpful to assist in the development and maintenance of social supports and networks. Occupational re-integration and support is important since work has a core role in most peoples lives.[380] Family or carer support may reduce relapse risk. Maintenance of social rhythm regularity, particularly with regard to sleep habits, is critical and should pertain to daily routines as well. Acting contrary to mood is an important component of this; when the person feels depressed and wishes to withdraw, pushing to maintain routine is generally helpful. Similarly, if the person feels elevated and capable of taking on far more than usual, they should be advised to stick to their routine. Exercise is of demonstrated value in depression and there are provisional data in bipolar disorder.[381] It is critical to address comorbidity, particularly substance misuse. There are data demonstrating that smokers have a poorer response to treatment and worse long-term outcomes,[382] and so consideration should be given to smoking cessation as part of routine treatment.[383]

5. Conclusions

The management of bipolar disorder has undergone many revisions in recent years as new agents and treatments have been developed and trialled with variable success. In conjunction with the advent of novel therapies and indications, there has been an increase in the understanding of the phenomenology and neurobiology of bipolar disorder that has made the classification and management of the illness necessarily more sophisticated. However, there remains a significant delay in detecting and diagnosing bipolar disorder, and a further need to improve treatments.

However, this paper has emphasized the need to be aware of recent advances and the emerging uses of new treatments in the management of bipolar disorder. It has also highlighted the importance of considering the limitations of evidence-based findings and the need for tailoring management to the individual. In particular, the successful treatment of bipolar disorder requires achieving prophylaxis and preventing relapse. In this regard, maintenance therapy is of paramount importance, and thus the tolerability of agents needs to be considered throughout treatment and should be factored into all management decisions. At the centre is the individual with bipolar disorder and the need to maintain a healthy therapeutic relationship. However, it is important to note that the evidence synthesized in this paper serves only as a guide to the management of bipolar disorder and that, in practice, all treatment recommendations require contextual interpretation, the consideration of local factors and the consultation of additional resources.

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