Bipolar disorder

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Bipolar disorder is a recurrent chronic disorder characterised by fluctuations in mood state and energy. It affects more than 1% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status. Bipolar disorder is one of the main causes of disability among young people, leading to cognitive and functional impairment and raised mortality, particularly death by suicide. A high prevalence of psychiatric and medical comorbidities is typical in affected individuals. Accurate diagnosis of bipolar disorder is difficult in clinical practice because onset is most commonly a depressive episode and looks similar to unipolar depression. Moreover, there are currently no valid biomarkers for the disorder. Therefore, the role of clinical assessment remains key. Detection of hypomanic periods and longitudinal assessment are crucial to differentiate bipolar disorder from other conditions. Current knowledge of the evolving pharmacological and psychological strategies in bipolar disorder is of utmost importance.

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Introduction

Fluctuations in mood are common in life, particularly when faced by stressful events. Nevertheless, when mood swings are striking and persistent, and result in notable distress or impairment, there could be an underlying affective disorder. Affective disorders can be classified along a spectrum defined by the extent and severity of mood elevation, from unipolar to bipolar II to bipolar I.[1] Individuals with unipolar disorder present with depressive episodes only, and those with bipolar II or I disorder show increasingly pronounced episodes of mood elevation.

Bipolar disorder affects more than 1% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status and represents one of the leading causes of disability among young people.[2] In a worldwide mental health survey,[3] the prevalence of bipolar disorders was consistent across diverse cultures and ethnic groups, with an aggregate lifetime prevalence of 0·6% for bipolar I disorder, 0·4% for bipolar II disorder, 1·4% for subthreshold bipolar disorder, and 2·4% for the bipolar disorder spectrum. Access for patients to mental health systems, however, differs substantially across countries, making management of this disorder especially difficult in low-income countries.[3] With respect to sex, bipolar I disorder affects men and women equally whereas bipolar II disorder is most common in women.[4]

Bipolar disorder is a lifelong episodic illness with a variable course that can often result in functional and cognitive impairment and a reduction in quality of life.[5,6] In WHO's World Mental Health surveys,[2] bipolar disorder was ranked as the illness with the second greatest effect on days out of role. Because bipolar disorder is mainly diagnosed in young adulthood, it affects the economically active population and, therefore, connotes high costs to society.[7] The onset of mania in later life might be indicative of an underlying medical comorbidity.[8] Because of the recurrence and chronicity of bipolar disorder, not only is acute treatment for management of mood episodes fundamental but also pharmacological and psychological approaches for prevention of further episodes are important.

In this Seminar, we discuss topics in bipolar disorder including clinical presentation, diagnostic classification systems, current knowledge about causes, prognosis across the lifespan, and pharmacological and psychological treatments. Furthermore, we include issues of particular interest, such as management of bipolar disorder in pregnancy and adolescence and monitoring. Finally, we address emerging trends in diagnosis and treatment and future developments.

Classification

Bipolar disorder, previously known as manic depressive illness, is a severe chronic mood disorder characterised by episodes of mania, hypomania, and alternating or intertwining episodes of depression (figure 1). No biomarker has yet been approved for diagnosis of any mental disorder and clinical criteria endure.[9] The most widely acknowledged diagnostic classifications are the 10th revision of the International Classification of Diseases (ICD-10)[10] and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[11]

Bipolar disorders are classified according to the longitudinal course, which is often characterised by the presence of subthreshold symptoms (panel).[12] Although bipolar I disorder might seem to have a more tortuous evolution and severe prognosis than bipolar II disorder because of cross-sectional symptom severity, bipolar II disorder has a high episode frequency, high rates of psychiatric comorbidities, and recurrent suicidal behaviours that impair quality of life.[13]

Search strategy and selection criteria

We searched PubMed between January, 1920, and June, 2015, with the term "bipolar disorder" in combination with the terms "diagnosis", "depression", "mania", "suicide", "childhood", "management", "acute treatment", and "long-term treatment". We restricted our search to English language publications. We largely selected reports from the past 5 years but did not exclude commonly referenced and highly cited older publications. We downloaded reports into Mendeley and scanned them for relevance to the topics selected for this Seminar. We also searched the reference lists of reports identified by this search strategy and selected those we judged relevant to the selected topics.

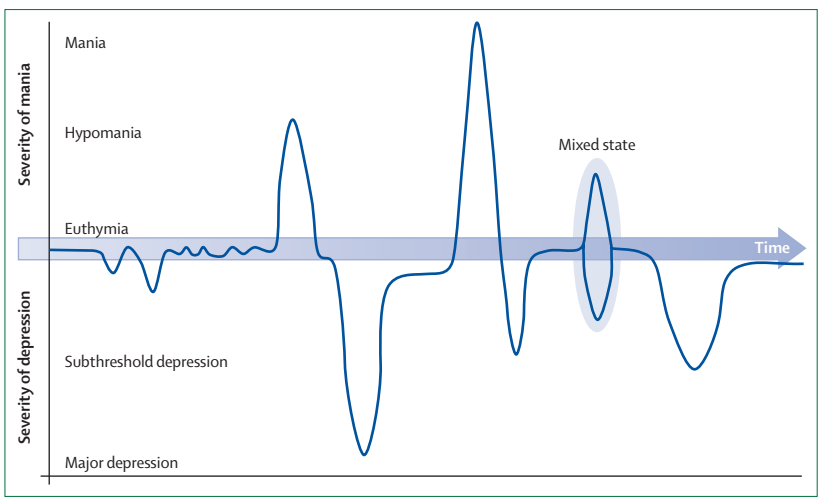

Figure 1: **Life chart showing progression of bipolar disorder**
Recording mood changes on a life chart can help clinicians to monitor and manage patients with bipolar disorder. According to severity, manic and hypomanic symptoms are registered above the state of euthymia (normal mood state) whereas depressive symptoms are depicted below.

Panel: **DSM-5 diagnosis of bipolar and related disorders**

Bipolar I disorder
At least one manic episode must be presented, although major depressive episodes are typical but not needed for diagnosis

Bipolar II disorder
At least one hypomanic episode and one major depressive episode are needed for diagnosis

Cyclothymic disorder
Hypomanic and depressive periods that do not fulfil criteria for hypomania or major depression for at least 2 years

Other specified bipolar and related disorder
Bipolar-like disorders that do not meet criteria for bipolar I disorder, bipolar II disorder, or cyclothymia because of insufficient duration or severity

- Short-duration hypomanic episodes and major depressive disorder
- Hypomanic episodes with insufficient symptoms and major depressive disorder
- Hypomanic episode without prior major depressive disorder
- Short-duration cyclothymia

Unspecified bipolar and related disorder
Characteristic symptoms of bipolar and related disorders that do not meet full criteria for any category previously mentioned

Substance or drug-induced bipolar and related disorder

Bipolar and related disorder due to another medical condition

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

Mania and hypomania

Manic or hypomanic episodes are states of elevated mood and increased motor drive that are finite in time and differ in severity and length. Although a manic episode impairs social or occupational functioning and might encompass psychotic symptoms or even lead to hospital admission, in a hypomanic episode, a disturbance in functioning can be seen by others but does not typically cause severe impairment or require admission to hospital. In some cases of hypomania, occupational functioning might even improve transiently because of heightened productivity and good humour. About 75% of patients with an acute manic episode present with psychotic symptoms.[14] Delusions can be mood-congruent in mania, with individuals displaying grandiosity, megalomania, or messianic ideation. However, mood-incongruent psychosis is not uncommon, with the flipside of perceptions of being envied, in jeopardy, and persecuted by their enemies.[14] Hence, psychotic features, even when mood-incongruent, do not rule out the diagnosis of bipolar disorder.

A hypomanic episode is defined in DSM-5 as persisting for at least 4 consecutive days, whereas a manic episode lasts for at least 1 week. The temporal cutoff of 4 days is not mirrored by a clear cutpoint in reported data, and some researchers have suggested that this period should be shortened to 2 days so that patients categorised with unipolar depression could be diagnosed with bipolar disorder.[15] Angst and colleagues on the multicentre, multinational, transcultural BRIDGE study[16] aimed to ascertain the frequency of symptoms of bipolar disorder according to DSM-IV-TR and the much broader bipolar-specifier criteria in patients seeking treatment for a major depressive episode. 903 (16%) of 5635 patients diagnosed with major depressive disorder fulfilled DSM-IV-TR criteria for bipolar disorder, whereas 2647 (47%) met the bipolar-specifier criteria. Thus, 31% of patients with a diagnosis of major depressive disorder had subthreshold hypomanic or manic symptoms with the broader criteria.[16] Without an objective marker, it is unclear if this finding represents underdiagnosis of bipolar disorder or false-positive diagnoses. In particular, basing diagnosis on very common and non-specific irritable states and rapid shifts in mood could risk abutting on borderline and related personality disorders and adjustment disorders.[17]

The reliability of phenomenology-based diagnostic systems such DSM-5, thus, remains controversial for diagnosis of bipolar disorder. The requirement to diagnose a manic episode only if the mood disturbance is accompanied by an increase in activity or energy, the hesitancy to change the length of hypomanic episodes in diagnostic criteria, and the introduction of the mixed specifier for affective episodes of any mood disorder—including unipolar depression—are still matters for debate. Other changes have been introduced to diagnostic criteria in recent times, such as consideration of bipolar diagnosis in manic or hypomanic episodes that emerge during treatment (eg, with antidepressants, corticosteroids, or electroconvulsive therapy) and persist at a fully syndromal level beyond the physiological effect of the treatment, and the application of DSM-5 specifiers.

Specifiers define clinical features of episodes and the course of bipolar disorder. For example, the rapid-cycling specifier describes the presence of at least four mood episodes that meet criteria for mania, hypomania, or major depression within 12 months,[18] whereas the mixed specifier defines episodes—either manic, hypomanic, or depressive—commingled with three symptoms of the opposite pole.[1] In previous editions of the DSM, the mixed specifier category was restricted to full manic episodes and, therefore, to a diagnosis of bipolar I disorder (panel). Both the rapid-cycling specifier and the mixed specifier are clinically important because they have been associated with a more severe prognosis, frequent and prolonged episodes, increased deaths by suicide, and additional comorbidity.[18,19] Creation of the diagnostic category "other specified bipolar and related disorder" in DSM-5 (panel) has impelled a lively debate between supporters[20] and detractors[21] about the decrease in the threshold for diagnosis of bipolar disorder and the embracing of the spectrum of bipolarity.

Under-recognition of hypomanic symptoms is, nevertheless, common. Patients do not always recall or read their mood accurately or judge its consequences, and sometimes they enjoy the mood state and view it as desirable. Nevertheless, hypomania often heralds a full-blown manic episode or depressive episode, with its subsequent burdensome outcomes. Although patients typically struggle with depression, families often complain about the results of hypomanic episodes. Thus, clinical acuity in detecting hypomanic periods is fundamental. Some scales assist in this task in general practice—eg, Hypomania Checklist 32 (HCL-32) is a screening method to identify hypomanic symptoms in patients with a major depressive episode.[22] Once a diagnosis of hypomania is confirmed, other scales are used to assess the severity of the hypomanic and manic episodes, such as the Young Mania Rating Scale (YMRS).[23]

Depression

At onset, most patients with bipolar disorder present with a depressive episode that differs subtly from unipolar depression.[24] DSM-5 criteria for a major depressive episode are the same for bipolar and unipolar depression, and severity of the episode is assessed with the same scales: the Hamilton Depression Rating Scale (HDRS)[25] or the Montgomery-Asberg Depression Rating Scale (MADRS).[26] The main difference between these two scales is that MADRS is more sensitive to change and does not emphasise somatic symptoms as much as does HDRS.

The symptomatic differences between unipolar and bipolar depression were first described in the 1950s by Leonhard[27] and validated a decade later by Angst,[28] Perris,[29] and Winokur and colleagues.[30] Although bipolar or unipolar depression do not have pathognomonic characteristics, these researchers described some clinical features that are useful to discriminate bipolar and unipolar depression. Bipolar depression usually has an earlier age of onset,[31] has more frequent episodes of shorter duration,[32] has an abrupt onset and offset,[33] is linked to comorbid substance misuse,[34] is triggered by stressors at early stages, and has more post-partum risk.[35] Atypical symptoms—such as hypersomnia, lability, and weight instability—are also common in bipolar depression,[36] being reported in 90% of episodes, but they are described in only half of unipolar depressive episodes.[37] Psychosis,[38] psychomotor retardation, and catatonia[39] are also more characteristic of bipolar depression, whereas somatic complaints are most frequent in unipolar depression.[40] A family history of mania is also a relevant indicator of bipolar depression.[41]

Suicide

People with mood disorders are at very high risk of death by suicide. The incidence of death by suicide among patients with bipolar disorder is high[42,43] and can be more than 20 times higher than in the general population,[44] particularly when bipolar disorder is untreated.[45] About a third to a half of patients with bipolar disorder attempt suicide at least once in their lifetime, and roughly 15–20% of attempts are completed.[46] Variables significantly associated with suicide attempts include female sex, young age at onset of illness, depressive polarity of first illness episode, depressive polarity of current or most recent episode, comorbid anxiety disorder, any comorbid substance misuse disorder, borderline personality disorder, and a first-degree family history of suicide.[46] By contrast, variables associated significantly with death by suicide include male sex and a first-degree family history of suicide. Prompt and comprehensive assessment and management of suicidal ideation in patients with bipolar disorder is needed. Assessment should include the intention to attempt suicide, availability and potential lethality of methods, and presence of protective factors.[47]

Diagnosis

Correct diagnosis of bipolar disorder is aided, to a substantial degree, by a directed interview with the patient and their relatives, to discern the longitudinal course of the disorder, which often differs from answers given in a cross-sectional interview situation. Only 20% of patients with bipolar disorder having a depressive episode are diagnosed with bipolar disorder within the first year of seeking treatment.[38] The mean delay between illness onset and diagnosis is 5–10 years.[48] The most common differential diagnoses—apart from major depressive disorder and schizophrenia—are anxiety disorder, substance misuse, personality disorder,[49] and, in children, attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder,[50] diagnoses that are typically comorbid with bipolarity.

Pathology

Knowledge of the pathogenesis and pathophysiology of bipolar disorder has progressed rapidly over the past few

decades. Although bipolar disorder is one of the most heritable psychiatric disorders, a multifactorial model in which gene and environment interact is currently thought to best fit this disorder.[51] Many risk alleles of small effect, which partly overlap with schizophrenia (eg, *CACNA1C*, *TENM4*, and *NCAN*) and are described in genome-wide association studies, contribute to the polygenic risk of bipolar disorder.[51] Historically, mood disorders were thought to result from an imbalance in monoaminergic neurotransmitter systems such as the serotonergic, noradrenergic, and—in particular in bipolar disorder—the dopaminergic neurotransmitter system. Despite evidence showing that these circuits are likely to play a part, no singular dysfunction of these neurotransmitter systems has been identified. Nevertheless, modulation of synaptic and neural plasticity seems to be important in the circuitry regulating affective and cognitive functions.[52] Neurotrophic molecules, such as brain-derived neurotrophic factor, have a vital role in signalling pathways of dendritic sprouting and neural plasticity.[53] Dendritic spine loss has been noted in post-mortem brain tissue of patients with bipolar disorder.[54] Other pathways that can affect neuronal interconnectivity are also under study, including mitochondrial dysfunction and endoplasmic reticulum stress, neuroinflammation, oxidation, apoptosis, and epigenetic changes, particularly histone and DNA methylation.[55] Because the core phenotype of bipolar disorder is a biphasic energy shift, corresponding monitoring of phasic dysregulation in mood, sleep, and behaviour is attracting attention. Awareness of the underlying molecular basis and neuroimaging changes, pathogenesis, and pathophysiology of bipolar disorder[56] is essential to discover novel drug targets and develop biomarkers of risk, prognosis, and therapeutic response.[57]

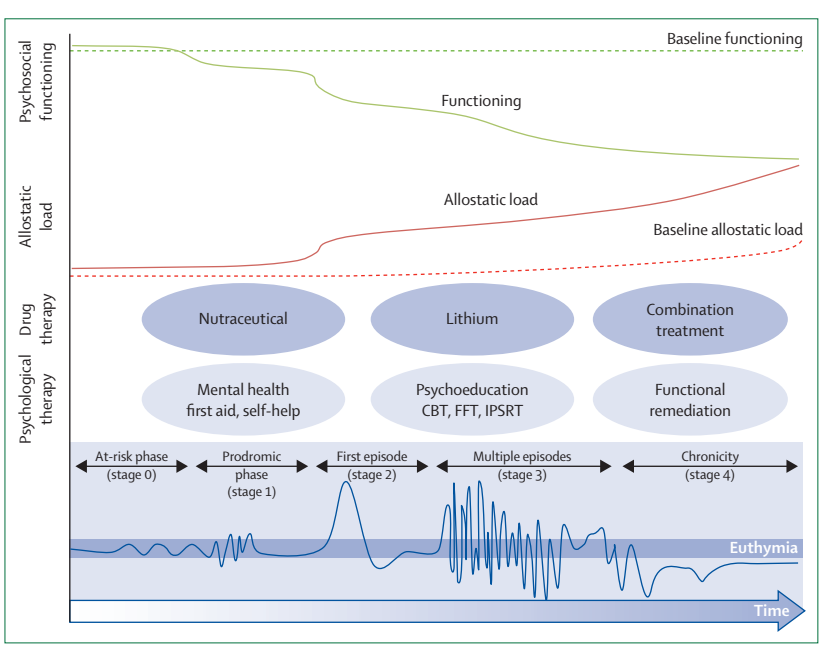

***Figure 2*: Neuroprogression of bipolar disorder**
During the course of bipolar disorder, psychosocial functioning begins to decrease in the prodromal phase, and premorbid functional levels are seldom reached. Meanwhile, allostatic load increases. Drug therapy helps to prevent episodes, and lithium could be especially helpful. Adaptation to adverse psychosocial or physical situations is facilitated by interventions such as mental health first aid and self-help, in particular in early stages. Psychoeducation, CBT, IPSRT, FFT, and functional remediation in patients with impairment are also useful in bipolar disorder. CBT=cognitive behavioural therapy. FFT=Family-focused therapy. IPSRT=interpersonal and social rhythm therapy.

Prognosis

The natural history of bipolar disorder often includes periods of remission, but recurrence is normal, particularly if adherence to treatment is poor. The polarity of the index episode can predict the polarity of subsequent episodes.[58] Patients with a depressive predominant polarity are most likely to attempt suicide, have a depressive onset, and be diagnosed with bipolar II disorder that follows a seasonal pattern.[59] Conversely, with a manic predominant polarity, drug misuse is common and patients usually present at a young age with a manic episode and have bipolar I disorder.[60] In a 15-year follow-up study, patients with bipolar I[61] and bipolar II[62] disorder had euthymia for about half the study period, with depression being the most prevalent mood state, reported during 31% and 52% of the study, respectively. Mixed episodes, hypomania, or mania were recorded for 1·6% and 10% of the study, respectively. Subsyndromal states were three times more common than full syndromal episodes.[61,62]

The notion of the progressive course of bipolar disorder, with its cognitive, functional, and medical aftermaths, was first described in 1920 by Kraepelin;[63] more recently, progressive modifications have been encompassed by the idea of neuroprogression (figure 2).[64] Despite patients with bipolar disorder having normal or even superior cognition before diagnosis,[65] in cognitive and neuroimaging studies,[66] bipolar disorder has been associated with subtle but substantial neurocognitive deficits across all mood states,[67] including periods of remission.[68] Poor performance in executive functions and verbal memory seems to be related not only to disease severity but also to the presence of psychotic symptoms, prolonged duration of illness, more manic episodes, and subsyndromal depressive symptoms.[69] This cognitive impairment could account, in part, for the functional impairment seen in patients with bipolar disorder even in remission.[70] Functional recovery unsurprisingly lags behind symptomatic or syndromal recovery.[71]

In addition to cognition and functioning, physical health is affected in patients with bipolar disorder.[72] Cardiovascular disorders, diabetes, and obesity are highly comorbid and arise earlier in the life course compared with the general population.[73] Medical comorbidities are indicators of a worse outlook for patients with bipolar disorder.[74] Mortality is also increased, with findings of a 30-year follow-up study showing that circulatory disorders and suicide are the main causes of death.[75]

Post[76] postulated the kindling hypothesis as a process of gradual sensitisation to stressors and individual's vulnerability to episode recurrence. Neuroprogression

overburdens adaptive mechanisms to stress (allostatic load), according to the allostasis hypothesis.[77,78] Because of the acknowledged gradual progression of bipolar disorder, and in view of the idea of neuroprogression, staging models have been proposed for bipolar disorder according to number of relapses[79,80] and functioning impairment.[80–82]

Treatment

The first step in the management of bipolar disorder is to confirm the diagnosis of mania or hypomania and define the patient's mood state, because the therapeutic approach differs considerably for hypomania, mania, depression, and euthymia. Diverse factors can affect pharmacological and psychological strategies; these include medical and psychiatric comorbidities, previous or current treatments, response to treatment or adverse effects in patients and relatives, and the patient's willingness to be treated. Clinicians should consider these factors, particularly in the initial treatment of an acute episode, to optimise efficacy, minimise the risk of adverse events and lack of adherence, and avoid switching of drugs.[83] In acute management, the primary goals are to ensure the safety of the patient and people nearby and to achieve clinical and functional stabilisation with minimum adverse effects. Moreover, engagement and development of a therapeutic alliance are important in any lifelong disorder that needs long-term adherence, and this collaboration is especially true during the first episode.[84] In long-term management, the main aims are to prevent recurrence of episodes and ensure functionality while optimising treatment. Guidelines have been published on the management of bipolar disorder,[85–88] which consider the latest developments in pharmacological and psychological treatments (table 1).

Acute management

Mood stabilisers and antipsychotics[89] are the mainstay of acute management of bipolar mania and depression. However, evidence for use of antidepressants to treat depression is unclear, and these drugs should never be used as monotherapy in bipolar I disorder.[90] Electroconvulsive therapy is highly effective for treatment-resistant acute mood episodes, particularly in patients with psychotic or catatonic features.[91]

Several comprehensive systematic reviews of the management of mania have been published.[92–94] With respect to efficacy, Cipriani and colleagues[93] reported that, overall, antipsychotics were significantly more effective for treatment of mania than were mood stabilisers, with haloperidol, risperidone, and olanzapine ranked as the most potent. With respect to acceptability, defined as how many patients stayed on the allocated treatment, quetiapine, risperidone, and olanzapine showed the best results. In general, risperidone and olanzapine had the best efficacy and acceptability. By contrast, Yildiz and co-workers[92] noted that discontinuation rates were lowest with aripiprazole, valproate, quetiapine, risperidone, and olanzapine, and no treatment was superior. In fact, sensitivity analysis by drug class indicated similar profiles for haloperidol, second-generation antipsychotics, and mood stabilisers. Nevertheless, in another study,[94] Yildiz and colleagues showed larger or quicker responses for various antipsychotics compared with lithium, valproate, and carbamazepine, with no differences between lithium and valproate or between second-generation antipsychotics and haloperidol. Antipsychotics might have a more rapid onset of action; haloperidol in particular seems to have a faster antimanic action compared with second-generation antipsychotics.[95] However, haloperidol has the substantive drawback of a greater risk of switching to depression and extrapyramidal side-effects.[96] Apart from these results, combination treatment with an atypical agent and a mood stabiliser has a higher response rate in manic episodes than does monotherapy with either drug.[97,98]

For management of depressive episodes, the pharmacological armamentarium is abridged compared with the wide options for mania. Despite the high prevalence and increased burden of depression, drug development in bipolar depression did not advance until the development of lamotrigine and atypical antipsychotics such as quetiapine, olanzapine, and lurasidone. One reason for this shortfall is the traditional off-label extrapolation of results from antidepressant trials in unipolar depression because of the dearth of specific drug trials in bipolar depression. In a meta-analysis of treatments for bipolar depression,[99] olanzapine plus fluoxetine, and quetiapine, were two of the most efficacious pharmacological therapies, whereas results for lamotrigine, lithium, and antidepressants such as paroxetine were variable. By contrast with the efficacy of lamotrigine for long-term treatment, evidence for its efficacy in acute management is less compelling. In an independent meta-analysis[100] of five industry-sponsored clinical trials of lamotrigine, modest beneficial effects were reported on depressive symptoms, with advantages in patients who were severely depressed. To what extent this finding reflects truly modest efficacy or methodological factors (the foremost being the need for a 6-week dose titration phase to full dose in mostly 8-week studies) remains unclear. With respect to lithium, findings of eight of nine small randomised clinical trials showed its efficacy in acute depression.[101] The risk:benefit profile of antidepressants is controversial and, therefore, the International Society for Bipolar Disorders (ISBD) convened a task force to seek consensus recommendations about their use in bipolar disorder.[102] They recommended serotonin reuptake inhibitors and bupropion in individual patients who might benefit, in particular, those with bipolar II disorder rather than bipolar I disorder, because the risk of manic switch is greater in patients with bipolar I disorder. Antidepressants should only be prescribed for individuals with bipolar I disorder as an adjuvant therapy with mood stabilisers.

	Clinical management			Advantages	Disadvantages
	Mania	Depression	Maintenance		
Mood stabilisers					
Valproate	+++	+	++	Useful in episodes with mixed features	CYP450 inhibitor, not recommended in women at childbearing age
Lamotrigine	−−−	++	+++	Depressive predominant polarity	Slow titration
Lithium	+++	++	+++	Antisuicidal properties	Not recommended in renal failure
Carbamazepine	+++	+	++	Effective in bipolar disorder with non-classic features	CYP450 inducer
Oxcarbazepine	+	+	+	Fewer adverse effects than carbamazepine	Hyponatraemia
Antipsychotics					
Aripiprazole	+++	−	++	Manic predominant polarity, good metabolic profile	Akathisia
Asenapine	+++	+	+	Possible treatment for depressive symptoms	Moderate metabolic syndrome
Chlorpromazine	++	−−−	+	Rapid efficacy	Risk of switch to depression, extrapyramidal symptoms
Clozapine	+	+	++	Resistant patients, few extrapyramidal symptoms	Agranulocytosis, sialorrhoea, postural hypotension
Haloperidol	+++	−−−	+	Rapid efficacy	Risk of switch to depression, extrapyramidal symptoms
Lurasidone	+	+++	+	Lack of anticholinergic effects	Efficacy related to feeding, akathisia, sedation
Olanzapine	+++	+++*	++	Rapid efficacy	Severe metabolic syndrome
Paliperidone	++	−	++	Can be administered intramuscularly every month, minimal liver metabolism	High doses are often needed
Quetiapine	+++	+++	+++	Only antipsychotic drug with indications for treatment of acute manic and depressive episodes and maintenance	Sedation
Risperidone	++	−	++†	Common intramuscular administration every 2 weeks	Risk of switch to depression, extrapyramidal symptoms
Ziprasidone	++	−	++	Manic predominant polarity, good metabolic profile	Efficacy related to feeding
Antidepressants	−−	+	+	Applicable in resistant bipolar depression combined with mood stabilisers	Risk of switch to mania
Electroconvulsive therapy	++	++	+	Recommended in pregnant women	General anaesthesia needed, anterograde memory loss

Reported clinical management reflects our interpretation of available evidence and does not necessarily imply regulatory endorsement. For further information refer to guidelines.[85-88] The table includes some clinically significant adverse effects that can be experienced by some patients exposed, which is by no means exhaustive and is not meant as a comparison between different drugs. +++=very highly recommended. ++=highly recommended. +=recommended. −=not much recommended. −−=not recommended. −−−=not at all recommended. *Olanzapine plus fluoxetine. †Risperidone longacting injectable.

Table 1: **Pharmacological management of bipolar disorder in mania, depression, and maintenance phases**

Novel treatments under assessment for acute management include armodafinil as an adjuvant treatment for major depressive episodes, modafinil as a cognitive enhancer, and ketamine for treatment-resistant depression. Drugs targeting pathways linked to oxidation (eg, *N*-acetylcysteine),[103] mitochondrial function,[104] and inflammation,[55] are also under study.

Long-term management

In view of the recurrent chronic nature of bipolar disorder, optimum long-term management is a preventive strategy that combines pharmacological, psychological, and lifestyle approaches from the first episode (figure 2).[105] In a network meta-analysis,[106] lithium was highlighted as one of the most effective treatments for the prevention of both manic and depressive episodes, despite lithium being associated with a decline in renal function, hypothyroidism, and hypercalcaemia.[107] Findings of the BALANCE study[108] showed that lithium monotherapy and a combination of valproate plus lithium were more likely to prevent relapses than was valproate monotherapy, irrespective of illness severity. Quetiapine has also been suggested as a suitable choice for long-term management of bipolar disorder,[106] but interpretation of data from the network meta-analysis should be done with caution because the quetiapine maintenance studies only included patients who responded to the drug during a previous acute episode. Moreover, findings of another meta-analysis[109] showed the efficacy of combinations such as quetiapine plus lithium or valproate. Once again, these results should be assessed with circumspection because treatments in most clinical trials were initiated after an acute episode.

Long-term therapeutic strategies differ according to the predominant polarity of the patient's bipolar disorder.[59] Whereas patients with manic predominant polarity have a better response to atypical antipsychotics, those with a depressive predominant polarity might respond best to lamotrigine and are more likely to need adjunctive antidepressants.[60,110,111] The polarity index is a metric to classify maintenance treatments from this perspective.[112] It divides agents between antimanic and

antidepressant prophylactic profiles. Quetiapine and lithium have a polarity index near to 1, indicating almost equal efficacy for prevention of manic and depressive episodes.

Pharmacotherapy, usually consisting of a mood stabiliser alone or in combination with an antipsychotic or antidepressant,[113] plus tailored psychosocial interventions in euthymia can decrease the risk of relapse, improve treatment adherence, and reduce the number and duration of hospital admissions.[114] There is some evidence that psychotherapy needs to be adapted to age or stage of illness, in particular for young people during their first episode.[115] Psychoeducation[116] has shown longlasting prophylactic effects in individuals with bipolar disorder.[117] Other useful treatments for patients include cognitive behavioural therapy,[118] interpersonal and social rhythm therapy,[119] and family-focused therapy.[120] Functional remediation has also shown efficacy in improving functioning in patients with bipolar I[121] and bipolar II[122] disorder with psychosocial functional impairment. Internet-based approaches are gaining traction.[123]

Special populations

Pregnancy

Bipolar disorder usually begins in early adulthood; therefore, female patients who are planning to start a family present the challenge of needing to administer drugs during pregnancy.[124] Preconception counselling and guidance are essential for women with bipolar disorder and their partners because some drugs are teratogenic, in particular during the first trimester. For example, valproate and carbamazepine increase the risks of spina bifida and low IQ[87] and should be avoided in women of childbearing age because of the risk of unplanned pregnancy. The risk of congenital malformations with lithium treatment might have been overestimated in the past, and evidence of teratogenicity after exposure to lithium is currently weaker than initially estimated.[125] The teratogenic risk of psychotropic drugs and the effect of an untreated mood episode on the mother and, consequently, the fetus should be assessed carefully, in particular after the first trimester, when the teratogenic risk of psychotropic drugs falls. Women whose mood is stable sometimes abruptly stop drugs when pregnant because of fears about potential teratogenicity. However, abrupt cessation can increase the risk of recurrence of a mood episode. Therefore, when drug withdrawal is indicated, it should be ceased gradually.[126] The risk of relapse is especially high in the post-partum period and for primiparous women; hence, reintroduction of treatment is strongly recommended after delivery.[35] Breastfeeding is usually not recommended in women with bipolar disorder who are taking pharmacological treatment.[127] All in all, careful planning and education of the woman and her partner are of utmost importance.

Adolescence

Bipolar disorder severely affects the normal development and psychosocial functioning of young people and increases the risk of suicide, substance misuse, and academic, behavioural, legal, and interpersonal problems.[128] Thus, early identification of this illness in children aged 13–19 years is crucial, because up to 60% of individuals with bipolar disorder present before age 21 years.[129] Moreover, careful attention should be paid to offspring of patients with bipolar disorder because they are at higher risk of developing the illness, which can occur at a younger age.[130] Diagnostic criteria for bipolar disorder in young people are the same as for adults, but diagnosis is more difficult in young people because a comprehensive longitudinal psychiatric assessment is needed, dovetailing with good knowledge of normal youth development and psychopathology. Cognitive and emotional immaturity in young people can restrict the verbal expression of mood symptoms, hindering ascertainment of key manic symptoms such as grandiosity, elation, and increased goal activity.[128] Moreover, young people with bipolar disorder tend to have mixed or rapid-cycling presentations,[131] and episodes of mania or hypomania are shorter than those recorded in adults.[132] Also, symptoms of mania and hypomania overlap with those of other common disorders in young people, such as ADHD, emerging personality disorders, and behaviour disorders, making differential diagnosis challenging. Irritability and temper outbursts are common manifestations across psychiatric disorders in young people, but to diagnose bipolarity, the presence of other manic or hypomanic symptoms and an episodic pattern are necessary.

Taking into account developmental issues, and until further research is available, treatment recommendations for adults also apply to young people.[85,133] Nevertheless, guidance should be used with caution until research in this area progresses. The scant available evidence for the management of bipolar disorder in young people is restricted to the acute treatment of manic and mixed episodes. Despite the fact that young people are more susceptible than adults to metabolic syndrome caused by use of antipsychotics, atypical antipsychotics might work better in this population compared with lithium and valproate.[134] Nevertheless, great care should be taken when prescribing antipsychotic drugs in young people, because of weight gain and an increase in body-mass index.[134]

Safety and monitoring

Medical comorbidities are highly prevalent in patients with bipolar disorder because of the adverse effects of pharmacological treatment, genetic vulnerability, and lifestyle factors (eg, smoking, poor diet, and lack of exercise). In view of the burden of these comorbidities and adverse drug reactions, regular monitoring of weight, glycaemia, dyslipidaemia, blood pressure, and liver function (table 2)[135] is indicated in patients with bipolar

	Dose or blood concentration	Monitoring
Mood stabilisers		
Valproate	50–150 µg/mL	Liver function, blood tests
Lamotrigine	50–200 mg/day	Hypersensitivity, dermatological reactions, liver function
Lithium	0·4–0·8 mmol/L	Renal and thyroid function, hydration
Carbamazepine	400–1200 mg/day	Liver function, hypersensitivity, dermatological reactions, blood tests
Oxcarbazepine	1200–2400 mg/day	Liver function, blood sodium
Antipsychotics		
Aripiprazole	5–30 mg/day	Akathisia, extrapyramidal symptoms, liver function
Asenapine	10–20 mg/day	Sedation, weight gain, glycaemia, dyslipidaemia, blood pressure, liver function
Chlorpromazine	25–800 mg/day	Extrapyramidal symptoms, liver function
Clozapine	50–450 mg/day	Absolute neutrophil counts, weight gain, glycaemia, dyslipidaemia, blood pressure, liver function
Haloperidol	1–40 mg/day	Extrapyramidal symptoms, liver function
Lurasidone	40–120 mg/day	Sedation, akathisia, weight gain, glycaemia, dyslipidaemia, blood pressure, liver function
Olanzapine	5–20 mg/day	Sedation, weight gain, glycaemia, dyslipidaemia, blood pressure, liver function
Paliperidone	3–12 mg/day	Weight gain, glycaemia, dyslipidaemia, blood pressure, liver function
Quetiapine	50–800 mg/day	Sedation, weight gain, glycaemia, dyslipidaemia, blood pressure, liver function
Risperidone	0·5–8 mg/day	Extrapyramidal symptoms, sedation, weight gain, glycaemia, dyslipidaemia, blood pressure, liver function
Ziprasidone	80–160 mg/day	QTc interval, liver function

Reported dose (or blood concentration) reflects our interpretation of available evidence and does not necessarily imply regulatory endorsement. For further information refer to guidelines.[85-88,135] The table includes some clinically significant adverse effects that can be experienced, which is by no means exhaustive and is not meant as a comparison between different drugs.

***Table 2*: Recommended dose or blood concentration and monitoring of common pharmacological treatments for bipolar disorder**

disorder. When administering lithium or valproate, blood concentrations should be monitored to ensure they are within the therapeutic range. Moreover, surveillance of renal and thyroid function is necessary because treatment with lithium has been associated with tubulointerstitial nephropathy, nephrogenic diabetes insipidus, and hypothyroidism.[135] Furthermore, hepatic function should be checked in patients receiving valproate and, in women, development of polycystic ovaries is possible. In aggregate, regular reassessment of the risk:benefit balance of each treatment is recommended in addition to consideration of other strategies when clinically significant adverse effects emerge.

Future directions

Bipolar disorder is a mental disorder that causes impairments in functionality of daily life, resulting in costs for both patients and society. It is a multifaceted disease, and a comprehensive biological, social, and psychological approach is mandatory. In the past decade, great progress has been made in the areas of molecular biology, genetics, and neuroimaging. The next step is to assimilate these results from a translational approach.[56]

A bidirectional bench-to-bedside plan of action is crucial. Strategies that seek to integrate biological, molecular, and neuroimaging data with clinical information are needed.[136,137] For instance, the essential roles of inositol monophosphatases, glycogen synthase kinase 3, the protein kinase C pathway, and calcium channels in intracellular signalling have been identified. Despite not being well validated at this stage, these molecular targets might act as starting points to develop future treatments.[105] Drugs acting through glutamate pathways, such as ketamine and its analogues, could be research opportunities for treatment of the depressive phase.[131] Areas of research that are generating great expectations include novel animal models, mitochondrial biogenesis, human stem cells derived from patients with bipolar disorder, optogenetics, proteomics, and metabolomics.

Progress from a translational perspective can enhance pathophysiological understanding[138] and could aid diagnostic accuracy, in particular in young people, to detect bipolar disorder at an earlier stage. Hopefully, objective biomarkers that represent underlying pathophysiological processes can be identified.[139] Staging models and strategies for personalised medicine are being investigated for their promise in increasingly precise biological and psychosocial interventions. In the near future, patients could receive combined pharmacological and psychological management specifically tailored to each stage of their illness and age. However, health-care systems might struggle with increasing costs of these elaborate approaches, despite their potential effectiveness, and more feasible strategies are proposed—eg, briefer and more efficient psychotherapy protocols.[140] This integrative approach could identify potential biological targets for novel drugs and personalised treatment in bipolar disorder.

Contributors
All authors planned the Seminar and, according to their area of expertise, contributed to the literature review and writing of the Seminar. All authors revised the Seminar for important intellectual content and approved the final version for submission.

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IG has received a research grant from Río Hortega Contracts (CM12/00062) and Juan Rodés Contracts (JR15/00012) at the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competiveness, Barcelona, Spain; has served as a consultant for Ferrer; and has been a speaker for AstraZeneca, Ferrer, and Janssen Cilag. MB has received research grants from the US National Institutes of Health (NIH), Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Foundation (MBF), National Health and Medical Research Council (NHMRC), Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier, and Woolworths; has been a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay, and Wyeth; and has served as a consultant to AstraZeneca, Bioadvantex, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, and Servier. BB has received research grants from the National Institutes of Mental Health and royalties for the publication of chapters and books from Random house, APA, and UpToDate. EV has received research grants, honoraria related to continuing medical education, or consulting fees from AstraZeneca, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Sunovion, Takeda, Centro para la Investigación Biomédica en Red de Salud Mental (CIBERSAM), Grups Consolidats de Recerca 2014 (SGR 398), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute.

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