The Essential Guide to Lithium Treatment

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Preface

More than 65 years after its discovery for the treatment of mania, lithium continues as the most valuable treatment option for bipolar disorder. In the areas of both basic pharmacology and in clinical efficacy, much has been discovered about lithium since its introduction into modern psychiatry in 1949. Lithium is an intriguing medication for several reasons: it is a simple element easily found in the periodic table, yet it has demonstrated a unique, striking efficacy in preventing mood episodes in patients with bipolar and unipolar mood disorders. For example, during the past 25 years, lithium's value as a suicide-preventing agent is increasingly acknowledged and has spurred new interest in its use. The ability of lithium to significantly reduce suicidal risk distinguishes it from the other mood-stabilizing agents currently available. Furthermore, basic research in the previous decade has demonstrated that lithium may possess neuroprotective properties in humans. These newer data suggest that lithium may even hold potential in preventing and treating dementia and other neurodegenerative diseases.

This book is a practical, up-to-date guide to the optimal use of lithium for the short- and long-term treatment of mood disorders. It is intended primarily for use by clinicians—physicians and other healthcare workers who use lithium to treat patients suffering from mood disorders. Thus, it addresses various aspects of effective and safe use of lithium in clinical practice. Among the subjects addressed are the pharmacology and mechanisms of action of lithium, its use for maintenance treatment, the role of lithium in the treatment of mania and depression and in suicide prevention, further clinical indications, the administration of lithium during pregnancy and the postpartum period, and adverse effects and their management. Relevant background information is provided on the diagnosis, classification, and natural course of mood disorders, and an overview of other treatments for bipolar disorder and major depression is included.

Despite the fact that lithium has unique properties as an effective mood stabilizer as well as demonstrating anti-suicidal and antidepressant effects, lithium is dramatically underutilized in the treatment of patients with mood disorders in many countries. In contrast, lithium is ranked consistently as a first choice medication for the long-term treatment of bipolar disorders in all major national and international treatment guidelines. So, the question is why is it underprescribed? Despite the considerable efficacy and advantages achieved by lithium, it remains a medication that, compared with most psychotropic medications, is slightly more difficult to

handle, largely due to its narrow therapeutic index. This factor, along with concerns about its tolerability and long-term renal risks, probably explains why lithium is underutilized. There is also the perception that the frequent and reliable monitoring of lithium plasma concentrations is difficult. However, when used properly, and reliable lithium plasma concentrations monitored, it is relatively well tolerated and not too complicated to administer at all. Among these factors, one other reason for its underutilization is that lithium is inherently a generic drug with no major pharmaceutical firm sponsor that would finance its global marketing. In contrast, many other treatments have each enjoyed a substantial period of patent protection, leading to intense marketing of the medication to psychiatrists and patients alike.

Both authors have more than 25 years of experience in research and clinical use of lithium. When used correctly, lithium unquestionably produces the most dramatic benefits of any medication in contemporary psychopharmacology. We have seen dramatic and often unique responses to lithium in many of our patients suffering severe and life-threatening mood disorders. Our main hope and goal, why we wrote this book, is that this practical guide to lithium treatment will be used much more often in clinical practice and will help patients and physicians.

We would like to acknowledge our patients who have taken lithium who have provided us with much of the knowledge, experience, and wisdom we have shared in this book. A special debt is owed to Bruno-Müller-Oerlinghausen and Paul Grof who taught MB how to use lithium in mood disorders. MG would also like to thank Jenna Gonzalez, and MB Daniela Jany, for the administrative help they provided with such cheerfulness.

Dresden, Germany — Michael Bauer
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Diagnosis and Classification of Mood Disorders

1

1.1 Introduction

The diagnostic syndromes of mania and depression have been given the general designation of mood disorder because mood disturbances are their core symptoms (Whybrow 1997). The basic nature of mood disorders is that they are episodic and recurrent, with discrete, symptom-free intervals. The most common classification scheme distinguishes between two main types of mood disorder, each having different gender, genetic, and course characteristics: when mania and depression occur, usually following each other in the same individual, the syndrome is called bipolar disorder (formerly manic-depressive disorder). Bipolar disorder is distinguished from unipolar illness, whereby one abnormal mood state, usually depression (major depressive disorder), occurs alone. Unipolar mania, in which individuals experience only manias in their life, is relatively rare compared to unipolar depression (Angst and Grobler 2015). Despite long-standing debate and conceptualization efforts, unipolar mania, including both pure mania and mania with mild depression, has not been integrated as its own diagnostic entity in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association 2013) or in the forthcoming revision of the International Classification of Diseases (ICD-11; due by 2018); it is subsumed under the category of bipolar disorder (Angst 2015).

When an individual suffers predominantly repeated depressions and only occasional mild mania (called hypomania), the diagnosis of bipolar type II disorder distinguishes the illness from the "classic" (manic-depressive) bipolar disorder type I. Figure 1.1 illustrates the mood changes over time in bipolar I disorder, bipolar II disorder, and major depressive disorder.

Most episodes of mood illness recover over time and with treatment, but there is a marked tendency for these disorders to recur (Geddes and Miklowitz 2013). At least 80 % of those who experience a manic episode are estimated to suffer one or more recurrences. In addition, subclinical symptoms may persist and the course becomes chronic. Despite their high lifetime prevalence of up to 3–4 %, bipolar

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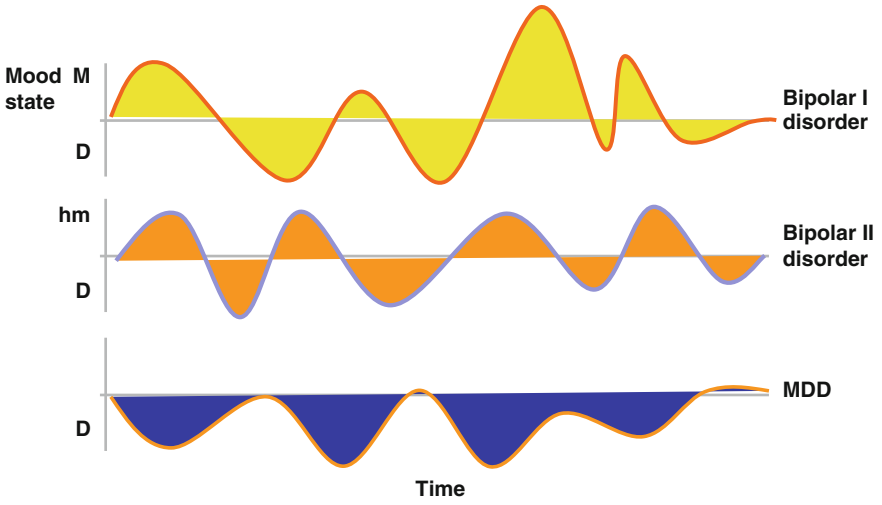

Fig. 1.1 Mood changes over time in bipolar I disorder, bipolar II disorder, and major depressive disorder (*MDD*). *D* depression, *hm* hypomania, *M* mania, *MDD* major depressive disorder

disorders are often misdiagnosed, leading to inappropriate or delayed treatments that have dramatic socioeconomic, professional, and familial consequences. Bipolar disorder typically evolves from an asymptomatic at-risk stage to the emergence of prodromal symptoms in adolescence or early adulthood, leading to an initial mood episode and eventually to an unpredictable and relapsing course throughout life.

1.2 Symptoms of Mood Disorders

The defining features of this group of disorders are affective disturbances with episodes of lowered mood and related symptoms (melancholic depression) and elevated and/or irritable mood with increased energy (mania). While the core symptoms of depression are sadness, loss of pleasure, and reduced energy, depression can present with many other and diverse symptoms. Sometimes the heterogeneity of depressive symptoms is referred to as "the different faces of depression."

1.2.1 Symptoms of Depression

In both ICD-10 and DSM-5, the essential feature of a (major) depressive episode is a period of depressed mood lasting at least 2 weeks revealing abnormalities in neurovegetative function (e.g., loss of appetite, weight changes, fatigue, sleep disturbances, e.g., insomnia, early awakening), psychomotor activity (agitation or retardation), cognitive changes (either distortions such as feelings of worthlessness, inappropriate guilt, and hopelessness), reduced cognitive capacity (such as decreased

concentration and ability to think), loss of energy and interest (apathy) in almost all activities, as well as anxiety and suicidal ideation. To qualify for the formal diagnosis, symptoms must be present most of the day and nearly every day, must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, and are not due to a physical/organic factor or illness (e.g., a drug abuse, a medication, a general medical condition). Furthermore, the occurrence of the major depressive episode cannot be not better explained by schizoaffective disorder, schizophrenia, delusional, and other psychotic disorders, and there has never been a manic or hypomanic episode. The diagnosis is made via a polythetic approach in which no one single symptom is required for the diagnosis.

1.2.2 Symptoms of Mania and Hypomania

Manic episodes are in many instances the opposite of depressions. Episodes of mania are characterized by elated or irritable mood or both, as well as related symptoms such as increased energy and reduced need for sleep, or hypomania, the symptoms of which are less severe or less protracted than those of mania. Specifically, in DSM-5, the essential feature of a manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day (nearly every day). The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning (such as job loss, dropping out of school, ruining a long-term relationship) or to necessitate hospitalization to prevent harm to self or others or having associated psychotic features. The episode is not attributable to the physiological effects of a substance or another medical condition.

The core distinction between mania and hypomania reflects the different levels of functional impairment. By definition, in DSM-5 hypomania is also characterized by a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least four consecutive days and present most of the day (nearly every day). The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic, and the disturbance in mood and the change in functioning are observable by others. However, in contrast to a manic episode, the episode is not severe enough to cause marked impairment in social or occupational functioning.

1.2.3 Symptoms of Mixed Episodes

Occasionally bipolar disorder reveals a mixture of manic and depressive symptoms referred to as a mixed state or mixed episode in DSM-IV. However, in DSM-5, the mixed episode diagnosis has been replaced by a mixed feature specifier. This new specifier “with mixed features” can be applied to the main bipolar subtypes

(bipolar I disorder, bipolar II disorder, and other specified bipolar and related disorders) but also to major depressive disorder. The change in DSM-5 was made to reflect the clinical phenomenon of mixed mood states that fail to meet all the criteria for a mixed episode of bipolar I disorder, reflected by the co-occurrence of full mania and major depressive disorder. In the new "mixed specifier," the predominant mood can thus be depression, mania, or hypomania. A lower threshold for mixed states will enable real-world admixtures of mood symptoms to be more easily captured (Malhi 2013).

1.3 Classification of Mood Disorders

There are two globally well-established classification systems commonly used in clinical practice, the aforementioned DSM-5 (American Psychiatric Association 2013) and the ICD-10 (World Health Organization [WHO] 1992). The fifth edition of DSM-5 is the 2013 update to the American Psychiatric Association's (APA) classification and diagnostic tool superseding the DSM-IV-TR published in 2000. In the United States, the DSM serves as a universal authority for psychiatric diagnoses, but it is also the ultimate global classification system for research studies. Treatment recommendations, as well as payment by healthcare providers, are often determined by DSM classifications in the United States.

ICD-10 is the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list drafted by the WHO (1992). It contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases. More than 25 countries use ICD-10 for allocating reimbursements and resources in their health systems. Even in the United States, the home of the DSM, there is increasing use of the ICD for billing and insurance purposes. There are substantial similarities between the two classification systems, but also some quite important differences.

1.3.1 Major Depressive Disorder

Major depressive disorder (unipolar depression) is associated with significant morbidity and mortality affecting individuals of all ages and races. The worldwide Global Burden of Disease study of the World Health Organization (WHO) has shown variations by country and region, but patterns and trends for depressive disorders are remarkably similar worldwide (Üstün et al. 2004; Murray et al. 2012). Major depressive disorder is characterized by a single or recurrent major depressive episode. The presence of anxiety can be very prominent both during an episode and between them, making it difficult to diagnose depression (Kupfer et al. 2012).

Major depressive disorder has a median lifetime prevalence of about 16 %. It occurs in about 5–10 % of the adult population during any 1-year period, with

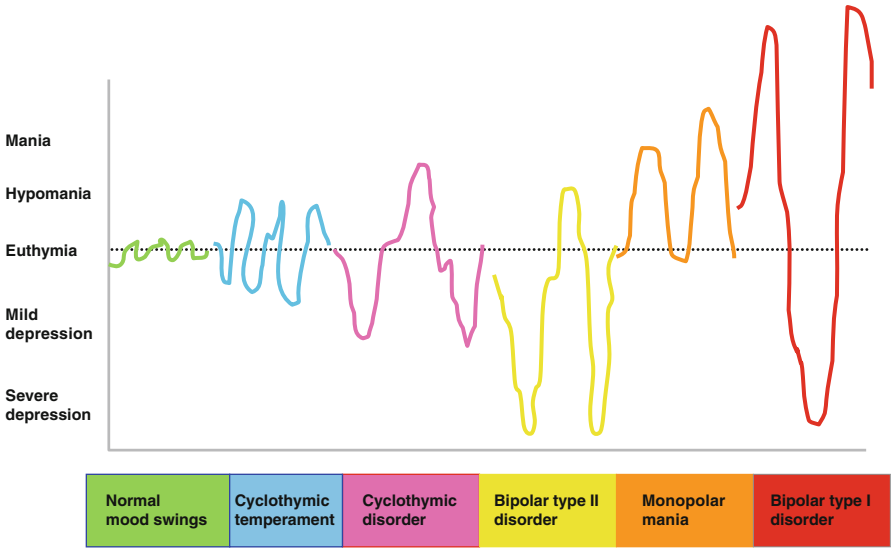

Fig. 1.2 Classification of bipolar spectrum disorders

women at higher risk than men (the ratio is approximately 2:1). At least 10 % of all patients presenting in primary care settings suffer from depression, with about 50 % presenting with predominantly somatic symptoms. Of all primary care patients with depressive symptomatology, about 25 % are classified as having major depressive disorder, 30 % as having minor depression, and 45 % as exhibiting nonspecific depressive symptoms. The latter two groups could be summarized as having "subthreshold" depression. Major depression can begin at any age, even in childhood and adolescence, but there are two peaks in the twenties and forties; the mean age of major depressive disorder's onset has been estimated as approximately age 30 (Angst and Preisig 1995).

1.3.2 Bipolar Disorder

Diagnostic criteria and definitions for bipolar disorder have changed over the past few decades. Most recently, bipolar disorder has been conceptualized as a continuum of phenotypes, ranging from normal mood swings to a pattern of mild depression and brief hypomania to one of severe mania and depression. This continuum concept of bipolar spectrum disorders is illustrated in Fig. 1.2.

The heterogeneity of bipolar disorder is reflected in the wide variation in related pathophysiological, genetic, and other biological and clinical findings. In the latest classification manual, the DSM-5, the designation "bipolar disorders" refers to a group of seven different subtypes, as shown in Table 1.1.

Table 1.1 Bipolar disorder subtypes in DSM-5

Bipolar I disorder: recurrent major depressive and manic episodes
Bipolar II disorder: recurrent major depressive episodes with hypomanic (milder than manic) episodes
Cyclothymic disorder: chronic (>2 years), fluctuating mood disturbance, involving numerous periods of mild hypomanic and depressive symptoms that do not meet criteria for a major depressive episode
Substance/medication-induced bipolar and related disorder
Bipolar and related disorder due to another medical condition
Other specified bipolar and related disorders
Short-duration hypomanic episodes (2–3 days) and major depressive episodes
Hypomanic episodes with insufficient symptoms and major depressive episodes
Hypomanic episode without prior major depressive episodes
Short-duration cyclothymia (less than 24 months)
Unspecified bipolar and related disorder: disorders with bipolar features that might alternate rapidly and do not meet the full criteria for any of the above disorders

1.4 How Common Is Bipolar Disorder?

The group of bipolar spectrum disorders considered together is very common and among the leading causes of disability in working-age adults. The lifetime prevalence of bipolar spectrum disorders was assessed in the National Comorbidity Survey Replication study in which a nationally representative sample of 9282 English-speaking adults were interviewed in the United States (Merikangas et al. 2007). Bipolar disorder type I (1.0 %) and type II (1.1 %) affect about 2 % of the population, with subthreshold forms of the disorder (bipolar spectrum disorders) affecting another 2.4 % (Merikangas et al. 2007). An international population-based study on the prevalence of bipolar spectrum disorders conducted by the WHO World Mental Health Survey Initiative (11 countries in the Americas, Europe, and Asia) found that the severity, impact, and patterns of comorbidity were remarkably similar across countries (Merikangas et al. 2011). In contrast to unipolar depression, bipolar disorder reveals no gender difference in its prevalence rate (the ratio is approximately 1:1).

1.5 When Does Bipolar Disorder Start?

Bipolar disorder may start at any time of life, but studies from many countries have reported three peaks in the distribution of the age of onset, occurring at about ages 17, 26, and over 40 (Leboyer et al. 2005). If the onset of symptoms occurs after age 60 years, the condition is usually secondary to other medical causes—e.g., neurologic (trauma, neoplasm, multiple sclerosis, epilepsy), endocrine (hyperthyroidism, Cushing's disease), infectious (AIDS), or inflammatory (systemic lupus erythematosus) disorders. Differences in the distribution of the age of onset have

also been reported among countries, although limited data are available from some world regions. Patients living in North America generally exhibit a younger age of onset than those living in European countries. In studies conducted in the United States, about 60 % of patients experience the onset of bipolar disorder before the age of 19, as compared to a third or less in many European countries (Post et al. 2008). Diverse factors may contribute to this variation in the age of onset. There is an agreement among researchers that both a patient's genetic makeup and methodological issues in defining onset contribute to the reported differences, and that the variability in the age of onset reflects the genetic heterogeneity underlying bipolar disorder (Bauer et al. 2014). A positive family history is one of the strongest predictors of early onset. However, in addition to the genetic component, both broad variability in the age of onset and the onset peaks occurring after puberty suggest that nongenetic factors may exert considerable influence. There is limited understanding of how nongenetic factors, such as socioeconomic status and the physical environment, may affect the expression of bipolar disorder, but recent research has shown that strong changes in the amount of sunlight in spring may have a significant influence on the age of onset (Bauer et al. 2015).

1.6 Why Is Bipolar Disorder So Difficult to Diagnose Precisely?

Many issues related to the identification, clinical presentation, course, and therapeutic management of bipolar disorders are unresolved and have been poorly studied. Bipolar disorders are often misdiagnosed, which leads to inappropriate, inadequate, or delayed treatments that can have negative socioeconomic, professional, and family consequences. Even when the diagnosis of bipolar disorder is established, management remains a major challenge, including how best to optimize treatment for an individual patient and how to balance the benefits and risks of medication treatment.

The typical trajectory of bipolar disorder involves the onset of subthreshold symptoms in adolescence and early adulthood, followed by the eventual emergence of a depressive, manic, or hypomanic episode. There is often a long interval passing between the initial symptoms and the correct diagnosis, followed by adequate treatment (Phillips and Kupfer 2013). It has been estimated that the mean delay between illness onset and diagnosis is 5–10 years. Many reasons contribute to the delayed diagnosis of bipolar disorder: considerable symptom overlap with unipolar depression, an overlooked history of hypomania, inadequate knowledge of bipolar disorder (in general medicine), and social and economic barriers for patients to access care.

A major reason making the diagnosis difficult is the challenge of differentiating bipolar disorder type I or II from unipolar depression, the latter being characterized by recurrent depressive episodes, especially in patients who present during a depressive episode and in those with no clear history of mania or hypomania. Unipolar depression is reportedly the most frequent misdiagnosis in patients with bipolar

disorder, especially bipolar disorder type II, because patients with this illness, by definition, never experience a manic episode. About 50 % of bipolar patients first present with a depressive episode, thereby making early diagnosis even harder.

With frequent misdiagnoses, patients often receive prescriptions for inappropriate or unnecessary medications that can potentially worsen symptoms and produce adverse effects. Assessing risk factors and recommending preventative measures for conditions such as diabetes mellitus are a routine part of clinical practice in medicine. However, there are no laboratory tests to help psychiatrists establish a diagnosis. The value of clinical risk factors is now being more closely examined.

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Natural Course of Bipolar Disorder and Implications for Treatment

2

2.1 Introduction

Understanding the natural history of any disorder, in this case bipolar disorder, is not just an academic exercise. Knowing the natural history is critical in order to create a treatment plan for patients that will minimize the amount of time spent ill and, as importantly, enhance both patients' ability to function and to boost quality of life. Therefore, before exploring the proper role of lithium in bipolar and other mood disorders, it is imperative to review the natural course of bipolar disorder and consider the different course trajectories in the construction of an individualized treatment plan. Natural history data derived from much older studies differ substantially from more recent studies. Although this may be due to a true evolution of the disorder, it may also reflect differences in definition and patient selection. For instance, the distinction of unipolar vs. bipolar disorder is relatively recent. Data from more than 50 years ago typically commingled these two diagnostic groups inevitably leading to differences in recurrence rates, age of onset, and so forth. This and other differences in definitions of psychopathology (described more fully below) certainly contribute to what seems to be a change in the natural history of bipolar disorder.

2.2 Natural History of Bipolar Disorder

Table 2.1 summarizes the core features of the natural history of bipolar disorder.

Bipolar disorder typically emerges in the late teens or early 20s, thereby making teenage bipolar disorder far from unusual (Merikangas et al. 2012). There is some evidence that the age of onset for bipolar disorder is lower in recent cohorts of patients than in older ones (Chengappa et al. 2003). This may reflect changes in diagnostic criteria or greater awareness of mood symptoms and their significance. If these were the main reasons, these findings would be considered as due to the artifacts of measurement and definition, not a true change in the expression of the

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Table 2.1 Core elements of the natural history of bipolar disorder

Early onset (age, 15–25 in most patients)
First episode—mania or depression (50 % each)
Overwhelmingly recurrent and lifelong
Cycle acceleration in *some* individuals, especially for the first three episodes
Depression predominance in most patients, especially in bipolar II
Mood episodes, both manias and depressions, may be triggered or spontaneous
Significant functional impairment
Suicide, equivalent to major depression, almost exclusively in depressed and mixed phases
Reduced life expectancy

disorder. It is also possible, however, that these changes reflect a genuine change in bipolar disorder and its onset. One hypothesis that may explain this is the greater use of antidepressants in children and adolescents which may then provoke the emergence of bipolar disorder at an earlier age than the natural history of the disorder without antidepressants would be. The phenomenon of genetic anticipation, in which those in later generations express both an earlier onset and a more severe form of the disorder, would also be consistent with the earlier age of onset seen in recent cohorts.

Neither the overall risk for bipolar disorder nor the age of onset differs by gender. Similarly, age of onset of bipolar I and bipolar II disorders is not different. Bipolar individuals with early onset—i.e., while teenagers—tend to have a worse course with higher rates of psychosis, rapid cycling, and comorbid substance abuse (Shulman et al. 2002). Here too, whether these early onset individuals have a more virulent form of the disorder or whether they have simply been ill longer with the attendant ravages from greater numbers of episodes, especially during developmentally sensitive periods such as adolescence, is unclear. A less typical but not rare type of onset for bipolar disorder is the emergence of the disorder after age 50. Compared to the early onset form of the disorder, those with later onset are less likely to have a family history of bipolar disorder and at higher risk to also have other neurological disorders, as if they suffered from a "secondary" bipolar disorder (Tohen et al. 1994). Not all later onset bipolar individuals show neurological histories; some simply have a later onset of the disorder.

Because only half of all bipolar patients have mania/hypomania as their first episode, the other half exhibit depression prior to the first mania/hypomania. Of course, in these situations, it is difficult to know whether the young person with a first depressive episode will continue as unipolar or will later emerge as bipolar. Clinical features that suggest that the individual with a first depression may be latently bipolar include psychotic features, early age of onset (since bipolar disorder generally begins earlier than does unipolar depression), sudden onset of the episode (like a "switch" which is more characteristic of the mood shifts of bipolar disorder), psychomotor retardation, and a family history of bipolar disorder.

The hallmark of bipolar disorder is its recurrent nature. Earlier studies from the nineteenth century and until the last 50 years found a substantial proportion of

bipolar individuals who suffered only one episode in a lifetime. As previously noted, these early studies "counted" episodes differently than we do currently. Older studies defined episodes by hospitalizations, thereby missing many mild to moderate outpatient mood episodes. Additionally, shifts in polarity, especially in continuous cyclers, would have counted as one episode in the distant past (since there was no intervening well period), whereas currently we would count a new episode with each polarity shift. Thus, in the past, an individual hospitalized for 10 years who suffered 30 manias and 30 depressions in a continuous manner would have been described as having had one episode, instead of the 60 episodes we would now count. More recent studies demonstrate that 85–95 % of bipolar individuals have a recurrence during follow-up periods ranging from 5 to 30 years (Goodwin and Jamison 2007). Of course, this still leaves a very small percentage of bipolar individuals who do not have recurrent episodes but these are the rare exceptions, not the rule. For clinical purposes, bipolar disorder should be considered virtually always recurrent. (Maintenance treatment is discussed in Chap. 5 [for lithium] and Chap. 13 [for other mood stabilizers].)

Earlier studies, in which maintenance treatment with lithium or other mood stabilizers did not alter the natural history of bipolar disorder (since these mood stabilizers either did not yet exist or were not used as routinely as they are currently), also suggested increased cycle frequency over time. Thus, the well interval between mood episodes shortened as the disorder progressed. The kindling model is partly based upon and is consistent with these observations as each episode lowers the vulnerability threshold for the subsequent episode. More recent studies, however, have been less consistent in demonstrating an increased frequency of episodes over time. What is likely is that the kindling model of increased cycle frequency applies in only some but not all bipolar patients. As an example, in a careful study of the natural history of bipolar individuals, approximately 50 % of bipolar individuals showed an acceleration of cycle frequency, and this was seen primarily over the first three episodes (Roy-Byrne et al. 1985). For the other 50 %, their cycle frequency was relatively constant starting with the first episode.

There is extraordinary variability in the sequence of bipolar episodes. Some bipolar patients tend to have biphasic episodes in which a mania is followed by depression (MDI [interval]) pattern or, conversely, depression is typically followed by a mania (DMI). With other patients, manias or depression may occur as single episodes not typically followed by an episode of the opposite polarity. Whatever the pattern, it tends to be characteristic of that individual such that polarity sequences will be replicated in most (but not all) subsequent episodes. Finally, a smaller subset of bipolar individuals shows a continuous cycling pattern with infrequent and brief euthymic periods.

The length of mood episodes also varies widely. It is surprisingly difficult to provide an accurate estimate of mean episode length since studies from the pretreatment era used different definitions, while more modern studies understandably rely on treated samples in which treatment will have (hopefully!) altered the natural course of the episode. In general, however, depressions have a slower onset but last longer than do manias.

Partly due to the ethical dilemma in the current era of having large numbers of bipolar patients treated with placebo for long periods of time, many studies over the last few decades have examined the course of naturalistically treated bipolar disorder. These data arise from a number of sources such as clinics that specialize in treating bipolar disorder in a number of different countries and from multicenter studies studying the natural history of treated bipolar disorder, such as the STEP-BD study in the United States. Patients from these samples tend to be sicker compared to those studies that have more rigid inclusion and exclusion criteria. Inherently, specialty clinics and academic medical centers tend to attract more complex and treatment-resistant patients. Thus, in contrast to the pharmaceutical firm-sponsored studies, these naturalistic samples include patients with more comorbidities of substance abuse, borderline personality disorders, and so forth. Additionally, naturalistically treated patients are, by definition, not treated in a uniform way. Some are treated with state-of-the-art medication(s) by their psychiatrists and others less so. Only some patients are treatment adherent in these samples. Some of these patients may be in evidence-based psychotherapy and others not. Despite the varied and uncontrolled nature of these patients and their treatments, the naturalistic studies provide a snapshot of bipolar disorder as seen in the community.

Ironically, despite the number of available bipolar maintenance treatments and their well-documented efficacy in preventing bipolar episodes (see Chaps. 5 and 13 for more details), recurrence continues to be the rule rather than the exception even in these recent naturalistically treated bipolar patients. Summarizing a number of studies, usual recurrence rates in these naturalistic samples of bipolar patients' range are 40–60 % over 1–2 years and 60–85 % within 4–5 years (Gitlin et al. 1995).

Additionally, bipolar disorder is associated with decreased life expectancy of at least a decade (Chang et al. 2011). This is due both to unnatural causes such as accidents and suicide and higher rates of comorbid medical disorders such as cardiovascular disease. At least some of the risk for comorbid heart disease can be attributed to the weight gain and metabolic syndrome associated with many psychotropic medications (McIntyre 2009).

2.3 Polarity Dominance in Bipolar Disorder

Although mania is the defining characteristic of bipolar disorder that distinguishes it from the other common form of mood disorders, unipolar depression, depression is the dominant pole of the illness. In recent studies of naturalistically treated bipolar disorder, individuals spent, on average, three times as much time depressed as manic/hypomanic (Baldessarini et al. 2010). Some but not all studies find that this ratio is skewed even more toward depression in bipolar II patients. As an example, one long-term study found that the average naturalistically treated bipolar II patient had a 39:1 ratio of depressed to hypomanic weeks over a follow-up period of more than 13 years (Judd et al. 2003). Since bipolar II patients in that study spent more than half the time symptomatic, these individuals averaged 5 days hypomanic compared to 197 days—over 6 months—depressed.

The idea of considering the ratio of manic to depressive episodes has given rise to the concept of predominant polarity, referring to the subgroups of bipolar individuals whose course is dominated by one pole or the other. Although varied definitions of this term have been proposed, predominant polarity may be simply defined by having at least twice as many episodes of one pole vs. the other (Popovic et al. 2013). Using this definition approximately half of bipolar patients will show predominant polarity (Carvalho et al. 2014a). (The other half, of course, have a more even distribution of episodes by polarity.) Manic predominant polarity is associated with earlier onset, bipolar I disorder, and a higher rate of substance abuse. Depressive predominant polarity is linked with bipolar II disorder, increased suicidal acts, and possibly female gender.

2.4 Episodic Versus Chronic Nature of Bipolar Disorder

The classic picture of bipolar disorder is that of an illness with discrete episodes, full recovery from episodes, and normal functioning and asymptomatic status between episodes. Unfortunately, recent studies have indicated that bipolar disorder is far more virulent than this classic picture would suggest. As noted above, one study found that bipolar II patients, followed naturalistically for over 13 years, were symptomatic more than 50 % of the time (Judd et al. 2003). Bipolar I patients were symptomatic just under 50 % of the time (Judd et al. 2002). Additionally, patients spent the majority of their symptomatic time in a subsyndromal state, meaning they would not meet formal criteria for a mania, hypomania, or depression but still experienced mood symptoms. Thus, bipolar disorder in the modern world is characterized by substantial amounts of time symptomatic with the boundary between symptomatic and euthymic times far less clear than was previously thought.

2.5 The Natural History of Rapid Cycling Bipolar Disorder

Rapid cycling bipolar disorder defines the subset of individuals, both bipolar I and bipolar II, who have more episodes per unit time than other bipolar individuals. The DSM-5 specifier defines rapid cycling by at least four episodes of either pole meeting the full-time criteria within 1 year (APA 2013). At any one time, between 15 and 35 % of bipolar patients meet criteria for rapid cycling with a mean just under 20 %. Lifetime prevalence of rapid cycling ranges between 26 and 43 % (Carvalho et al. 2014b).

The natural history of rapid cycling bipolar patients varies from transient to chronic. For some patients, it constitutes a “bad patch” of illness in which they experience more instability and more mood episodes than usual. Whether due to treatment or the natural evolution of the disorder, rapid cycling in these patients dissipates over time. Consistent with this, one naturalistic study found that when bipolar patients who cycled rapidly in the previous year were followed naturalistically for 5 years, the vast majority did not continue to exhibit rapid cycling (Coryell et al.

1992). For a smaller group of patients, however, rapid cycling continues over years and defines a more brittle, sensitive, and more difficult to treat subgroup of bipolar disorder.

2.6 Stress and the Course of Bipolar Disorder

Even though bipolar disorder shows many qualities of a predominantly biological disorder with its strong genetic diathesis, response to biological treatments, and so forth, it is equally clear that the course of bipolar disorder and the precipitation of mood episodes are profoundly affected by environmental variables. These variables may be psychological/interpersonal stresses such as disruptions in important relationships or termination from a job or moving from one home to another but may also include more biological environmental triggers such as sleep deprivation or changing time zones. In evaluating the effect of stress on the emergence of a new episode, it is important to be cautious since it is too easy to attribute a causal effect from a random occurrence. Additionally, it is relevant to distinguish between truly independent life events such as the death of a loved one or natural disasters from events that are dependent on the person's behavior. Examples of the latter might be the breakup of a relationship as a consequence of manic or depressive behaviors or a car accident caused by manic impulsivity or speeding. The relationship between the life event and a mood episode may include both dependent and independent factors. As an example, a bipolar individual with a spontaneously occurring episode may get fired due to inappropriate behavior at work (a dependent event) and then became more manic due to the lack of structure and the financial stress of being unemployed (an independent event). Overall, examining the issue prospectively, thereby avoiding retrospective distortions, bipolar patients are more likely to experience a mood episode after an independent event than at other times in their lives (Johnson et al. 2008). Some, but not all studies, find that episodes earlier in the course of bipolar disorder are more likely to be associated with a stressful life event than episodes later in the disorder.

Another consideration associated with higher risk of a mood episode is that of chronic stressors such as a difficult family environment. Those bipolar patients living with a stressful family have been shown to relapse more quickly and more often than those in more benign supportive families (Miklowitz et al. 1988).

The most important of the nonpsychological stresses that may trigger mood episodes are those related to circadian rhythms. These are particularly important since they are generally not considered stresses, commonly occur, and are easily prevented or managed. Of these, sleep deprivation and crossing time zones are the most critical. Bipolar patients should be instructed not to go without sleep since sleep deprivation is well established as a trigger for manias but not depressions (Barbini et al. 1996). Examples of normative behavior associated with sleep deprivation are students studying all night or young people partying all night. With airplane flights in which many time zones are crossed, bipolar patients should ensure that they sleep at least some hours and pay attention to medication adherence.

Finally, childhood trauma, with its attendant biological perturbations, is a risk factor for the development of bipolar disorder (Aas et al. 2016). Childhood trauma is associated with a generally more severe mood disorder such as an earlier age of onset, greater risk of rapid cycling, increased suicidality, and a greater likelihood of comorbid substance misuse (Etain et al. 2013).

2.7 Functional Outcome in Bipolar Disorder

During most of the modern era, outcome in psychiatric research, including that of mood disorders, used symptoms and syndromes (which are simply the co-occurrence of symptoms within a certain time frame) as their end points. For acute treatment, the usual questions were: What was the response or remission rate, as defined by a previously determined change score or a score below a certain threshold within a certain time period? For maintenance treatment in which the goal is the prevention of episodes, parallel questions would be: What percentage of patients had an episode recurrence? What was the mean length of time until another mood episode? These outcome measures are critical since the more symptomatic patients are, the more their lives will be adversely affected by their illness.

Yet, the choice of symptoms and syndromes as our primary outcome measure also reflects the ease of measuring symptoms using reliable and not overly complex rating scales. Unfortunately, symptoms are a rather crude measure of outcome. Another method of measuring outcome would be function, using the overall meaning that we would all apply to our lives and those around us. Function measures the ability to perform the core roles in a life as defined by one's culture. This definition would include both primary role function—school/work/childcare/taking care of the house—and social/interpersonal function. All functional rating scales include at least one measurement of each of these domains. Although a number of reliable and valid functional outcome rating scales are available, no one scale has become the standard analogous to the Young Mania Rating Scale for manic symptoms.

Since Kraepelin's landmark distinction between mood disorders (manic-depressive insanity) and schizophrenia (dementia praecox), it has been clear that mood-disordered patients had a better overall prognosis, especially in function and life trajectory. Schizophrenia was generally considered to show a progressive downhill course, while mood disorders were episodic with full recovery between episodes. Crudely, this generalization is true: mood disorders, including bipolar disorder, have a better long-term prognosis compared to schizophrenia. However, all recent studies demonstrate that bipolar disorder is characterized by profound functional impairment in all spheres (Judd et al. 2008). Despite the occasional bipolar individual whose unusual creativity and productivity have led to fame and/or unusual financial success, bipolar disorder is more typically associated with lower socioeconomic status with high rates of unemployment and days missed at work (Schoeyen et al. 2011). Interpersonally, bipolar disorder is similarly associated with higher rates of separation, divorce, and relationship distress (Coryell et al. 1993). Additionally, family members who are often called upon to aid bipolar relatives show high levels of distress related to their roles as caregivers.

A critical issue surrounding functional impairment in bipolar disorder is understanding the factors associated with this negative long-term outcome. This would, of course, enhance the possibility of creating treatment options—or using available treatments more vigorously—to combat the functional impairment. The most obvious factor leading to greater functional impairment in bipolar disorder is the number of mood episodes and, even more, the cumulative time spent in mood episodes (Gitlin et al. 1995). This makes intuitive sense since the burden of symptomatic periods pervasively interferes with both role performance—work, school, and home responsibilities—and the quality of interpersonal relationships. What is less intuitive is that depressive symptoms and episodes contribute more to functional impairment than do manic/hypomanic periods. Furthermore, subsyndromal depressive symptoms—depressive symptoms that are not severe enough to be considered as part of a major depressive episode—play a dominant role in long-term functional impairment (Altshuler et al. 2006).

Other than symptoms, especially depressive ones, the other important factor correlating with poor function in bipolar disorder is cognitive impairment. Even when euthymic, bipolar individuals consistently show a broad-based cognitive impairment, cutting across all cognitive domains evaluated (Bourne et al. 2013). Of course, not all bipolar individuals show cognitive impairment. Presumably, cognitive impairment has a greater negative impact on primary role functioning—school and work—than on social functioning. The etiology of the cognitive impairment is assuredly multifactorial. It may be an intrinsic part of the disorder, analogous to the cognitive dysfunction seen in schizophrenia. In some patients, medications may play a role in reducing cognitive performance, although most studies find that medications play a very limited role. Other factors that may explain some of the cognitive impairment in bipolar disorder include the effect of comorbid disorders such as substance abuse, psychosis, and the cumulative effect of depression.

The treatment implications of the functional impairment seen in bipolar disorder are obvious on one hand and unstudied on the other. The most important implication is to aggressively pursue euthymia since those with greater illness burden show greater impairment. Second, if depression, especially subsyndromal depression, is associated with greater functional impairment, then bipolar depression needs to be treated more vigorously. Chapter 7 reviews the efficacy of lithium in bipolar depression, while the overall topic of bipolar depression is reviewed elsewhere (Bauer et al. 2012). Finally, a more direct approach to treating cognitive impairment is needed. Both pharmacological approaches and cognitive remediation approaches (as have been investigated in schizophrenia) should be considered.

2.8 Quality of Life in Bipolar Individuals

Another method of measuring outcome which is less common than those that are symptom based or function based reflects quality of life (QOL), which measures the more general sense individuals have of their lives—i.e., do they feel satisfied or fulfilled? Quality of life is therefore more subjective than either symptom-based or

function-based measurement since the latter two evaluate individuals according to some objective (albeit culturally determined for function) standard, while QOL is entirely based on the individual's subjective appraisal of their lives. A subset of QOL, called health-related quality of life (HRQOL), refers to those aspects of an individual's life that impact directly upon their health. HRQOL may be affected by factors such as side effects from psychotropic medications, leading to the likely possibility of patients improving in symptom-based measures and even functional measures while rating themselves lower on HRQOL scales due to sexual side effects, sedation, weight gain, and so forth. Even more than functional outcome, given the inherent subjectivity in its definition, there is no consensus on the optimal rating scales to use in measuring QOL. Additionally, mood states, especially depression, are likely to affect QOL measures. Therefore, QOL measures need to be obtained during euthymic periods to avoid simply measuring the cognitive distortions associated with mood states.

Not surprisingly, bipolar patients score lower than control populations on QOL measures (Michalak et al. 2005). This is especially so in those who are evaluated while depressed. Even manic/hypomanic patients tended to rate their QOL low; whether this reflects the common admixture of depressive symptoms within manic states is not yet clear. For HRQOL, again, depressive states correlated with lower scores. Unintuitively, bipolar patients rated themselves lower on HRQOL than did those with unipolar depression (IsHak et al. 2012).

2.9 Bipolar II Disorder

As discussed in more detail in Chap. 1, compared to individuals with bipolar I disorder, those with bipolar II disorder have, by definition, milder episodes of mania called hypomania. However, to describe bipolar II disorder as an *overall* milder disorder is incorrect. As noted above, in one systematic long-term outcome study of naturalistically treated patients, bipolar II individuals spent more time symptomatic than did bipolar I individuals (54 vs. 47 %; Judd et al. 2002, 2003). Although bipolar I patients have higher rates of hospitalization compared to bipolar II individuals due to the inherent severity of full-blown manias, depressive episodes may be more common in bipolar II individuals (Vieta et al. 1997). Additionally, bipolar II patients attempt suicide as frequently as do bipolar I patients (Novick et al. 2010).

2.10 Suicide in Bipolar Disorder

The most feared long-term outcome for all mood disorders including bipolar disorder is suicide, which is discussed in greater detail in Chap. 8. As has been well documented, depression—both unipolar and bipolar—is associated with the highest risk of suicide of any psychiatric disorders. The comparative suicide rates of unipolar and bipolar disorder vary by study and population but, examining all the studies, may reasonably be considered approximately equal. It must also be acknowledged

that at least some of the unipolar depressed patients who commit suicide may have been undiagnosed bipolar II patients. Bipolar individuals are at higher risk for suicide early in the course of the disorder, regardless of the patient's age (Ösby et al. 2001). Greater amounts of mood cycling as well as rapid cycling are risk factors for both suicidality and completed suicide within a bipolar population.

It is surprisingly difficult to accurately estimate the suicide rate among current bipolar populations. Earlier studies suggested an extraordinarily high rate in the range of 15–20 %, which is much higher than rates derived from more recent studies. A number of factors likely explain the decreased suicide rate seen in more modern studies. These include: (1) Many of the earlier studies followed only previously hospitalized mood patients who, by definition, have a more severe illness than those who have never been hospitalized. (2) Earlier studies frequently confused proportionate mortality, defined as the percentage of suicides among those who have died vs. case fatality which is the percentage of patients followed for a certain time period who commit suicide (Palmer et al. 2005). Because young people die infrequently from medical causes, studying a cohort of young bipolar individuals will overestimate the suicide rate if proportionate mortality rates are used. (3) The possibility/probability/hope that treatment of bipolar depression and maintenance preventive treatment may treat and prevent the types of symptoms and episodes within bipolar disorder that give rise to suicidality (Angst et al. 2006). Specifically, as will be discussed in detail in Chap. 8, lithium has been convincingly shown to decrease suicidality in both bipolar and unipolar patients.

More recent rates of suicide among bipolar individuals are in the 5 % range (Tondo et al. 2003). This is far in excess of the risk in the nonpsychiatrically ill population. As an example, the standardized mortality ratio for suicide among bipolar individuals has been estimated to be at least 15 × greater than anticipated (Harris and Barraclough 1997).

As expected, the risk of suicide among bipolar individuals is highest during the depressed phase of the disorder. Approximately 10 % of bipolar suicides occur during mixed manic states in which the combination of depressed mood, irritability, and heightened energy confers a particularly high suicide risk (Isometsa et al. 1994). In one study, higher rates of suicide attempts among bipolar individuals compared to those with major depression were partly explained by the 65 times higher rates during mixed manic states, seen by definition only in those with bipolar disorder (Holma et al. 2014). Suicides during euphoric manias are rather rare. Deaths during manias are more typically the consequence of excessive risk-taking behavior without the intent of ending one's life.

2.11 Treatment Phases in Bipolar Disorder

Given the nature of bipolar disorder—acute episodes of both mania/hypomania and depression—and the inherently recurrent nature of the disorder, an optimal treatment plan would include both acute and maintenance strategies. The three phases of treatment of bipolar disorder (as with many other psychiatric disorders) are (1) acute, (2) continuation, and (3) maintenance.

Acute treatment is used to alleviate actively occurring symptoms. For bipolar patients, this would equate to treating acute mania and hypomania (covered in detail in Chaps. 6 and 13) and acute depression (see Chaps. 7 and 13). If the treatment approach is effective, acute treatment of mania or depression ranges between 6 and 12 weeks. Maintenance treatment is described in detail in Chap. 5.

The goal of continuation treatment, the treatment phase with the fewest studies, is to prevent a relapse into the same episode for which treatment was begun. Continuation treatment begins when the patient is considered to be recovered from the acute mood episode. With this definition, the end of acute treatment and the beginning of continuation treatment would require the patient to achieve remission, not response, from the acute episode. Using rating scales, remission would be defined by a score below some cutoff score in either mania or depression scales, in contrast to response which is defined by a percentage (typically 50 %) improvement. Remission is not equivalent to being truly asymptomatic but to being predominantly back to one's baseline state.

Conceptually, the length of continuation treatment should relate to the length of the natural history of the episode. Thus, continuation treatment after an acute mania should generally be considered to be shorter than after an acute bipolar depression (since the latter episodes generally last somewhat longer). Given the episode length data summarized above, continuation treatment for acute mania should be approximately 4 months, while for depression, 6 months would be reasonable.

There is an astonishing paucity of studies evaluating the proper length of continuation treatment with *any* psychiatric disorder, including bipolar disorder. No controlled studies on the proper length of continuation treatment after a manic episode or bipolar depressive episodes have been published. Therefore, the conceptual considerations just noted should be used.

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Lithium and Its History

3

3.1 What Is Lithium?

Lithium is a natural trace element found in small amounts in all organisms including plants and animals. Lithium is eluded from rock and soil and accumulates in groundwater. The element serves no apparent vital biological function since animals and plants survive in good health without it. It is not even known whether lithium plays a physiological role in any of these organisms, but nutritional studies in mammals have indicated its importance to health, leading to the suggestion that it be classed as an essential trace element. Observational studies in Japan suggested that naturally occurring lithium in drinking water may lengthen the human life-span (Zarse et al. 2011).

Therapeutic doses of lithium to treat psychiatric and other medical disorders are more than 100 times higher than natural daily intakes. Lithium's therapeutic applications in medicine are unique and intriguing for one important reason: how can a "simple" element have such profound effects in humans by demonstrating unique, striking efficacy in many patients with bipolar and unipolar mood disorders?

3.2 A Fascinating Element: Lithium's Discovery

Lithium was discovered in 1800 by a Brazilian chemist in a mine on the island of Utö, Sweden. Because it was not found free in nature, but rather in rocks and mineral springs, it was given the Greek name *lithos,* meaning stone (Fig. 3.1).

Since its discovery 200 years ago, lithium has been used in medicine in one form or another for almost 150 years. Within the first decades after its discovery, it was utilized to treat various medical conditions including gout, urinary calculi, diabetes, infections, and rheumatism, but with no confirmation of any major effects in these diseases (Schou and Grof 2006).

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Fig 3.1 Spodumene—a pyroxene mineral consisting of lithium aluminum inosilicate, LiAl(SiO3)2, a source of lithium

3.3 Early Applications and the Breakthrough in Psychiatry

It did not take long for lithium to also be used experimentally in psychiatry. The Danish physiologist Carl Lange published in 1886 a monograph entitled "On periodical depressions and their pathogenesis." In this work he described his and his brother's use of a lithium-containing mixture to prevent the periodic occurrence of severe depressions. The modern history of lithium started in 1949 with John Cade's contribution after he noted its specific effect in patients with mania (Cade 1949). In the late 1940s, Australian psychiatrist Cade sought a treatment for "psychotic excitement" (manic-depressive illness). He suspected that a normal metabolite circulating in excess in the body was the cause of the illness. Cade injected lithium *urate* intraperitoneally into guinea pigs and noticed that they became calmer and less responsive to stimuli without becoming drowsy. Later, he observed in his experiments that lithium *carbonate* exerted the same effect on the guinea pigs. He concluded that the lithium ion, and not uric acid, must have been responsible for the observed effects. Subsequently, Cade imagined that lithium might also be helpful in treating psychiatric patients with agitation. Before using lithium carbonate in his patients, Cade tried it on himself for a few weeks. He observed no ill effects and embarked on a clinical trial in groups of psychiatric patients: he gave lithium to ten of his manic patients and observed remarkable results. All ten manic patients responded, their symptoms improved clearly, and the symptoms returned when lithium therapy was discontinued. These dramatic findings were reported in a 1949 issue of the Medical Journal of Australia (Cade 1949), a journal not widely distributed in the world at that time.

Cade later experimented with the therapeutic potential of elements resembling lithium such as rubidium, cesium, and strontium, but although some of his findings seemed promising, they were not followed up systematically (Schou and Grof 2006).

Cade's discovery triggered a series of reports in other countries that confirmed lithium's calming effects on manic excitement. In 1954, the Danish psychiatrists Mogens Schou and Erik Strömgen confirmed Cade's findings of lithium's "antimanic" effects by conducting a trial designed to be partially double-blind (Schou et al. 1954).

Following Schou's report from 1954, in the 1950s through the mid-1970s, a series of trials evaluating the efficacy of lithium in acute mania were published. The methodology of these studies was not consistent with the usual prerequisites for modern acute treatment trials such as randomization and placebo-controlled methods. Furthermore, in these early studies, outcome was often evaluated in accordance with personal impressions without the systematic rating scale measures currently used. Despite these design drawbacks, lithium seemed to be a consistently effective antimanic agent.

A later trial by Baastrup and Schou (1967), again in Denmark, involved the long-term administration of lithium to patients suffering from frequent recurrences of bipolar disorder. In most of them, lithium treatment led to a clear reduction in recurrences of mania and depression and in some patients to the complete disappearance of mood episodes. Figure 3.2 provides a diagram of impressive case histories from the classic first report on lithium's prophylactic efficacy by Baastrup and Schou (1967).

The use of lithium (as monotherapy) expanded beyond its administration for bipolar disorder to other indications (e.g., schizophrenia, schizoaffective disorder, alcoholism; see Chap. 9), but revealing much less efficacy.

In the 1970s, the widespread clinical use of lithium proceeded with the Danish physicians' pioneering research. Their important findings were gratefully accepted by doctors in many countries because they revealed for the first time an effective medication-based treatment for this serious and devastating, sometimes fatal illness to prevent future depressive, and manic episodes (Schou and Grof 2006). The administration of lithium to treat mania was finally approved by the United States Food and Drug Administration (FDA) in 1970. Shortly thereafter, in 1974, this application was extended to its use as a preventive agent for manic-depressive illness. However, the therapeutic use of lithium in North America (in the United States in particular) was slow from the beginning, which may have been the result of the fact that lithium was unavailable for patent (with no commercial interest) and initially cautious usage due to poisonings that occurred in the early days (Gershon and Daversa 2006). New concerns appeared shortly thereafter when the first investigations of renal function and signs of lithium-induced chronic nephropathy were published (Hestbech et al. 1977). The renal effects of long-term treatment with lithium remain a concern and are discussed in detail in Chap. 12.

Fig. 3.2 Diagrammatic presentation of case histories from the classic first report on lithium's prophylactic efficacy (Reprinted with permission from Baastrup and Schou (1967))

3.4 Lithium's Discovery: Also a History of Controversies

In the history of modern psychopharmacology, few medications have genuinely changed the outlook, prognosis, and sense of optimism for patients suffering major mental disorders. Lithium is one of these medications. Even now, more than 60 years after its discovery, lithium remains one of the most valuable medications for the treatment of mental disorders. However, the history of lithium use in psychiatry reveals varying degrees of acceptance in different countries, as well as controversy. Especially in England, some physicians maintained that the evidence as available at the end of the 1960s insufficiently supported the claim of lithium's prophylactic efficacy (Blackwell and Shepherd 1968). In some countries, including the United States and the United Kingdom, resistance to the use of lithium was slowly overcome due to doubts about its efficacy, troublesome side effects, and a few fatal cases due to its inappropriate usage in the early years of treatment. This early skepticism (Blackwell and Shepherd 1968) was at least partly dispelled by controlled clinical trials, exemplified by the seminal trials conducted by Prien and his colleagues in the United States in the early 1970s (Prien et al. 1973). In the United States especially, lithium became more widely accepted in the 1970s, largely through the research and other efforts by Samuel Gershon, Baron Shopsin, and Ronald Fieve (Gershon and Daversa 2006).

Recent randomized placebo-controlled trials have demonstrated that concerns about the validity of the early pivotal trials were ill founded; they have substantially increased the body of randomized evidence (Chap. 5). Since then, the evidence base has grown substantially, particularly through lithium's use as active comparator in pivotal trials of new medications.

Worth noting is lithium's gradual decrease in use by the late 1980s in conjunction with the advent of anticonvulsants and atypical antipsychotics. Lithium use has declined continuously in the United States relative to Europe and other parts of the world since the early to mid-1990s. Many psychiatrists, especially those trained in the last 10 years, have never prescribed lithium (reinforcing their mistaken belief that it is too difficult to use) and feel insecure in their ability to prescribe it effectively.

3.5 Position in Treatment Guidelines

Since the discovery of lithium in modern psychiatry, lithium has been mainly considered as a prophylactic treatment for bipolar disorders and a treatment for acute mania. Lithium has received lesser attention for its potential value in treating and preventing acute depressive episodes in unipolar depression. Two recent systematic reviews and meta-analyses on lithium's efficacy compared to placebo and other treatment options demonstrated its clear efficacy in preventing mood episodes (Miura et al. 2014; Severus et al. 2014). It has since been argued that lithium be recommended as *the* single preferred first-line drug in the long-term treatment of bipolar disorder (Nolen 2015). This is in line with the recommendation in the British

NICE (National Institute for Health and Care Excellence 2006) guideline that lithium, given its evidence base from trials with a non-enriched design and due to its relative safety, should be the *sole* first-line treatment.

Another use of lithium has been as an augmenting agent of antidepressants, currently among the best-evidenced augmentation therapies in the treatment of depressed patients who do not respond to antidepressants (Chap. 7). In several leading international guidelines, there is an agreement regarding the role of lithium in treating major depressive episodes: lithium augmentation is considered a first-line treatment (e.g., National Institute for Clinical Excellence [NICE; National Collaborating Centre for Mental Health 2010], World Federation of Societies of Biological Psychiatry [WFSBP; Bauer et al. 2013]; British Association for Psychopharmacology [BAP; Cleare et al. 2015]).

3.6 Renaissance of Lithium Treatment?

Quite similar to another "old" medicine—aspirin—with a history of more than half a century of discovering its different effects, many new aspects of lithium's effects and efficacy in psychiatry and the neurosciences have been discovered in basic and clinical research since its introduction into modern psychiatry in 1949. For example, during the past 20 years, lithium's value as a suicide-preventing agent is being increasingly acknowledged and has spurred new interest in lithium's use. Its ability to significantly reduce suicidal risk may distinguish it from the other mood-stabilizing agents currently available (Lewitzka et al. 2015). Furthermore, basic research in the previous decade revealed that lithium may possess demonstrable neuroprotective properties. These new data suggest that lithium may hold potential in preventing and treating dementia and other neurodegenerative diseases (Chap. 9).

Many experts in the field are convinced that lithium still is a tremendously underutilized drug in the treatment of patients with mood disorders. Kay Redfield Jamison once stated "Lithium is not an easy drug, but neither are mania and depression easy illnesses to have or to treat" (Jamison 2006). Among other factors, another reason for its underutilization is that lithium is inherently a generic drug with no major sponsor that would finance its global marketing. In contrast, many other treatments (Chap. 13) have each enjoyed a substantial period of patent protection, leading to intense marketing of the medication to psychiatrists and patients alike. However, lithium remains an indispensable element in contemporary psychopharmacology and an essential medication in the treatment of patients with mood disorders.

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What Is Lithium and How Does It Work? 4

4.1 Chemistry of Lithium

Lithium is a chemical element symbolized by *Li* carrying atomic number three in the periodic table. It is a soft, silver-white metal belonging to the alkali metal group of chemical elements and has—beyond medical indications—several industrial applications, e.g., in heat-resistant glass and ceramics, and lithium-ion batteries.

Because lithium is highly reactive, it is usually stored in mineral oil (paraffin). As a medication, it is always used as one of its salts, for example, lithium carbonate, lithium sulfate, or lithium citrate. It is the lithium part of the salt, the lithium atom, that is effective, and it does not matter which salt is used; no clinically relevant differences have been found among the different lithium salts in clinical studies.

As described earlier in Chap. 3 on lithium's history, lithium is an unusual and unique medication for the treatment of mood disorders because it is a chemical trace element, a small atom with unique pharmacological and chemical properties (Birch 2006). It is not known whether lithium plays a physiological role in humans. Since it is a simple element, one might think that lithium acts by a simple mechanism. The opposite is probably true; yet after more than 60 years of widespread clinical use, we still do not know exactly why lithium works so well for many patients suffering from mood disorders (Malhi et al. 2013). Table 4.1 summarizes important clinical aspects of lithium therapy that may be most relevant when investigating which molecular actions of lithium could be responsible for its clinical effects.

Nevertheless, during the past decade, new evidence has expanded our understanding of how lithium might exert its mood-stabilizing properties in individuals suffering from bipolar disorder. As a result of novel insights into the mechanisms by which lithium might work, research has demonstrated that lithium induces its cellular and molecular effects, at least partially, by activating neurotrophic and neuroprotective pathways and their associated signaling mechanisms (Quiroz et al. 2010).

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Table 4.1 Clinical factors that could provide clues to mechanisms of action of lithium

What we do know
Lithium is effective in preventing mood episodes and reduces the risk of suicide
The response to prophylactic treatment runs in families
Most patients need plasma levels between 0.6 and 1.0 mEq/l for a full clinical effect in maintenance treatment
Lithium works best in patients with classical (typical) features of bipolar disorder
Lithium does not lose efficacy over time (even decades)
Lithium is neuroprotective in vitro and probably in vivo as well
What we assume
Various of lithium's clinical effects may be independent
Lithium may work better early in the course of illness
Rapid discontinuation of lithium may raise the risk of relapse
Responders to lithium differ from responders to other mood stabilizers
Lithium works in augmentation treatment of major depression with all antidepressants (including the more recent selective compounds, e.g., SSRIs)
What we do not know
How long does it take for lithium to exert its prophylactic effect?
Is the mechanism of action the same for all patients?
Is the neuroprotection essential for mood stabilization?
Are partial responders distinct from "excellent" responders?

Modified from Alda (2015)

4.2 Pharmacokinetic Properties of Lithium

Pharmacokinetics is the study of what the body does to a drug and includes its absorption, distribution, and elimination. Lithium's pharmacokinetic properties differ greatly from those of other medications (Fig. 4.1).

Unlike other medications, lithium it is not metabolized or bound to proteins in the blood because it is chemically an element. After oral intake, it is absorbed rapidly within the gastrointestinal system and eliminated almost exclusively via the kidneys in a manner mostly dependent on serum levels (Alda 2006; Malhi et al. 2012). At therapeutic lithium blood levels (e.g., 0.8 mEq/l), the lithium concentration in the brain is about 0.4 mEq/l (the ratio of brain/blood lithium level is approximately 0.5:1; Soares et al. 2001). Food does not alter lithium absorption, and thus most patients prefer to take lithium after meals to reduce the gastrointestinal irritation that may otherwise occur.

With standard lithium preparations, peak levels occur in 1–3 h, and absorption is complete after 6–8 h. In healthy young subjects, lithium's elimination half-life is 18–24 h. Of note, since lithium is excreted exclusively through the kidneys, renal function is a central determinant of its half-life. Since renal function inexorably declines with age, lithium's half-life lengthens significantly with age. This translates to the common observation that, as patients get older (>55 years), the dose required to maintain a steady serum level decreases substantially (sometimes by more than

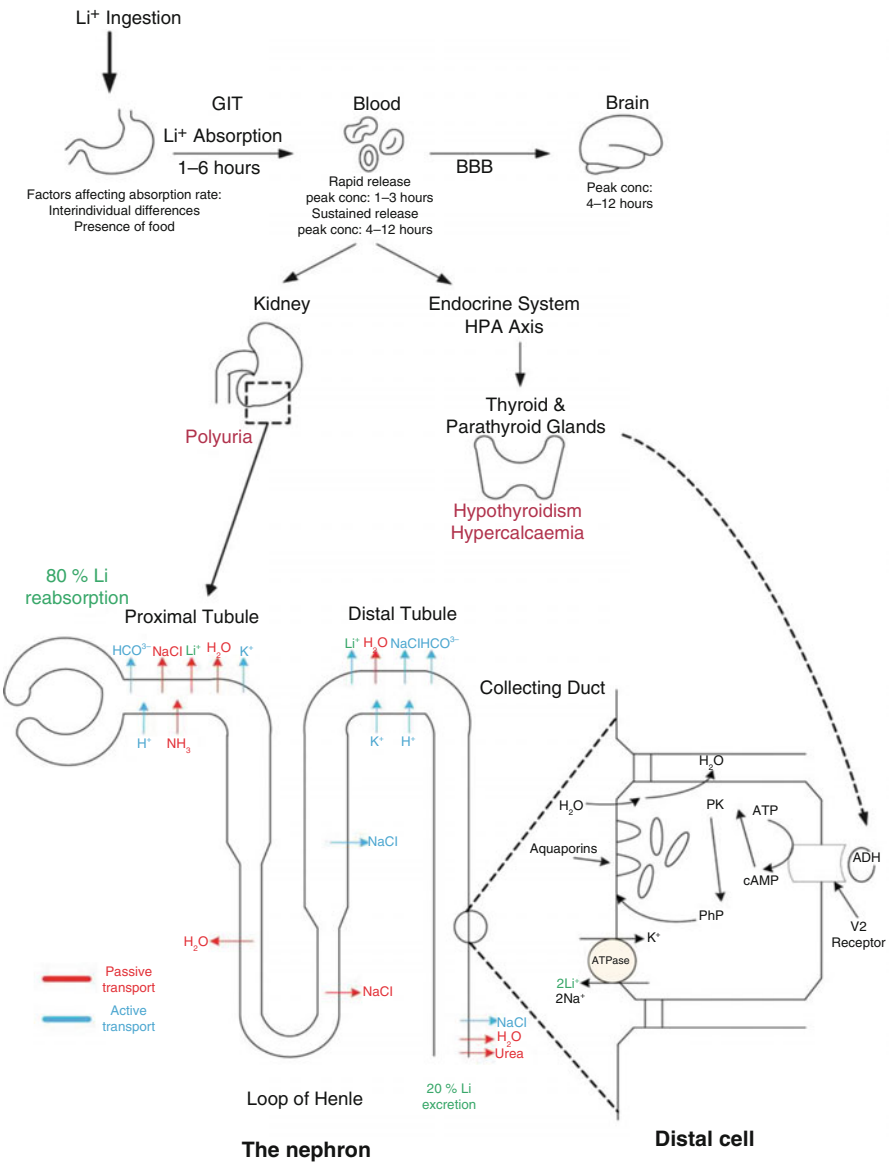

Fig. 4.1 Pharmacokinetic and pharmacodynamic actions of lithium: the effects of lithium on particular organs in the body as well as its movement through the nephron (With permission reprinted from Malhi et al. 2012)

50%). Some elderly patients (e.g., 75+ years of age) may attain therapeutic lithium levels with daily doses as low as 150–300 mg (amounting to 50% or less than standard therapeutic doses). This warrants more careful and closer monitoring of lithium blood levels, co-medications, and somatic illnesses in patients older than 55 years.

To understand the behavior of lithium in the body, it is helpful (although simplistic) to remember that it is handled biologically in a manner resembling sodium's. Most significant from the pharmacokinetic point of view is the potential of several commonly used drug classes to inhibit lithium's elimination and thus increase lithium plasma levels. These drugs include diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs—the most prominent members in this group of drugs are aspirin and ibuprofen, standard medications to reduce pain and fever), and ACE inhibitors (medications to treat high blood pressure). Their use in lithium-treated patients warrants caution (for more details, see Chap. 11).

Because lithium is rapidly absorbed from the gastrointestinal system, high peak serum levels (relative to other pharmacokinetic parameters such as the 12 h level) occur. Therefore, lithium preparations using *slow-release (sustained) formulations* to reduce the postabsorption peaks of plasma levels have been developed. Peak levels occur 4–12 h after the ingestion of lithium-sustained formulations. Such preparations may help patients prone to gastrointestinal distress or other transient side effects (e.g., tremor) secondary to temporary increases in lithium serum levels. In contrast, the slower absorption may contribute to variable bioavailability of lithium, for instance, in clinical conditions involving faster gastrointestinal passage. Another point to keep in mind is that 12 h levels in patients on slow-release lithium are close to peak levels and may be more susceptible to random variation, making laboratory monitoring more difficult (Fig. 4.2; Alda 2006).

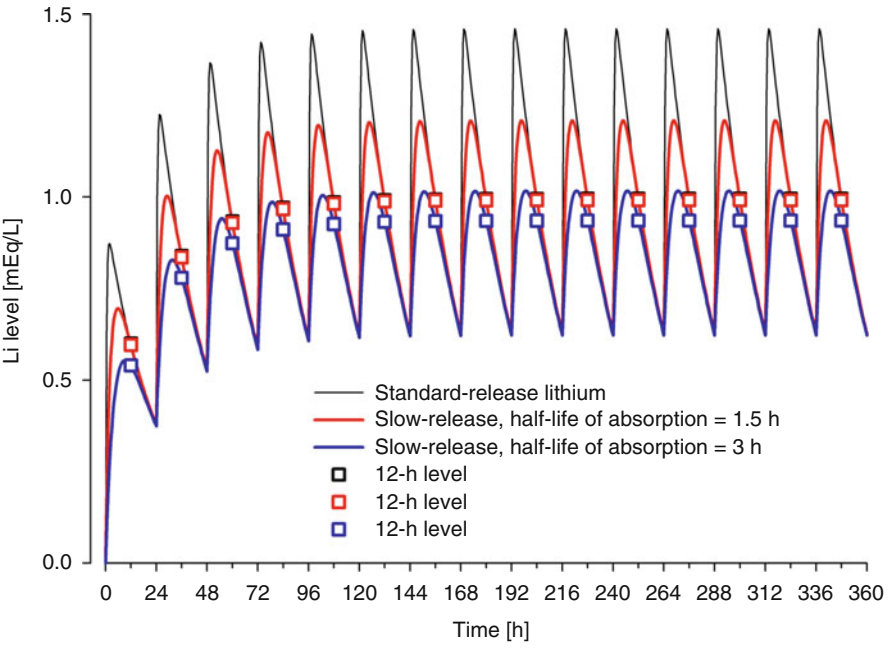

Fig. 4.2 Effect of absorption rate on the course of lithium plasma levels (With permission reprinted from Alda 2006)

In recent years, clinical practice has also shifted toward a *once-daily dosage* because most patients tolerate such a regimen well and feel more comfortable. Furthermore, when given in a single daily dose, lithium treatment may be associated with less polyuria and reduced renal concentration capacity (Plenge et al. 1982; Bowen et al. 1991). These are important factors leading to better adherence to medication. However, clinicians prescribing a once-daily dosage should keep in mind that standardized 12 h levels will be higher in conjunction with the same amount of lithium given once a day than with divided dosing. The recommended (therapeutic) 12 h lithium levels are based on studies that assume a divided (twice-a-day) dosage. It is not entirely clear whether such levels might be subtherapeutic for those taking lithium only once daily (Alda 2006).

4.3 The Principal Pharmacodynamic Actions of Lithium

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body and describes the mechanisms of drug action. After decades of research that began soon after the discovery of lithium's effects in mania, its mechanism of action in preventing recurrences of bipolar disorder is still only partially understood and largely remains a mystery (Alda 2015). Lithium has multiple pharmacological effects on multiple signaling pathways and other cellular processes. Lithium research is complicated by the absence of specific animal models of bipolar disorder and by the necessity of relying on in vitro studies of peripheral cell tissues. A number of distinct hypotheses emerged over the years, but none has been conclusively supported or rejected (Malhi et al. 2013).

Lithium's pharmacodynamic actions are multifaceted and are now understood as being even more complex. The common theme emerging from pharmacological and genetic studies is that lithium affects multiple steps in cellular signaling. Unlike most other established psychopharmacological agents such as antidepressants and antipsychotics, lithium does not bind to cellular receptors; instead, it appears to exert a multitude of therapeutic actions by modifying intracellular second messenger systems downstream of metabotropic neurotransmitter receptors, via enzyme inhibition with subsequent alteration of a complex and interconnected intracellular enzymatic cascade (Brown and Tracy 2013). Nonetheless, when trying to dissect lithium's various mechanisms of action, two enzymatic pathways have emerged during the past decade as its targets: inositol monophosphatase (IMPase) within the phosphatidylinositol (PI) signaling pathway (Berridge and Irvine 1989) and the protein kinase glycogen synthase kinase-3β (GSK-3β) (Ryves and Harwood 2001). These enzymes need magnesium (Mg^{2+}) to bind at circumscribed metal ion binding sites for activity. Lithium inhibits these enzymes by inhibiting the physiological cofactor Mg^{2+}, a vital regulator of numerous signaling pathways.

These two distinct major enzymatic pathways (PI and GSK-3β) altered by lithium might be a common mechanism of action, although the precise contribution of each to clinical effects is not yet known. It is also possible that the numerous therapeutic

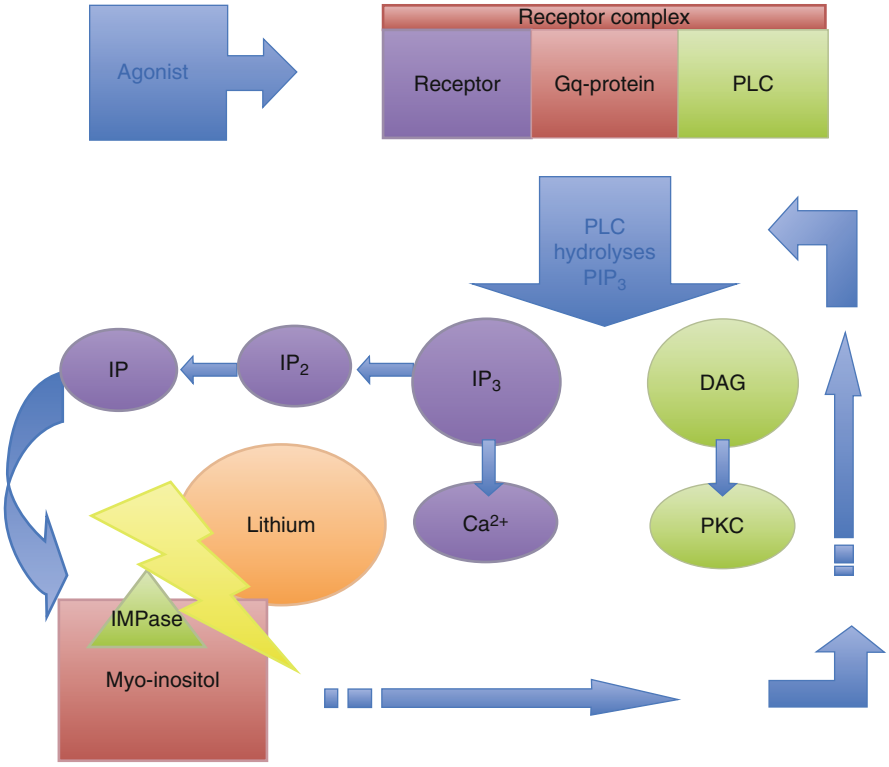

Fig. 4.3 Inositol depletion within the phosphatidylinositol (PI)-signaling pathway (With permission reprinted from Brown and Tracy 2013). An agonist binds to a receptor complex, consisting of a receptor, Gq-protein, and phospholipase (PLC). PLC hydrolyzes the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) to form two second messengers: inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). IP3 binds to specific receptors to help open the calcium (Ca^{2+}) channel, and DAG initiates activation of protein kinase C (PKC). IP3 is sequentially broken down into inositol bisphosphates (IP_2) and then inositol monophosphates (IP). IP is finally broken down into myoinositol by the enzyme inositol monophosphatase (IMPase). Lithium inhibits IMPase, leading to myoinositol depletion. Myoinositol is also the substrate for synthesis of phosphatidylinositol (PI), which is phosphorylated to form mono-, bis-, and tris-phosphatidylinositol. Lithium-induced myoinositol depletion therefore prevents the resynthesis of PIP2 and subsequent regeneration of IP3 and DAG, affecting cell signaling (Brown and Tracy 2013)

lithium effects on biochemical systems may be due to effects further downstream of these two main mechanisms (Figs. 4.3 and 4.4) (Pasquali et al. 2010).

Such downstream effects are the attenuation of amplitudes of cyclic AMP formation, modulation of the activity of the phosphatidylinositol-derived second messenger system, modification of the activity of transcription factors regulated by GSK-3, and subsequent alterations in gene expression of several gene products important in the regulation of excitability and resilience of neural cells (van Calker 2006).

Consistent with this preclinical evidence, lithium can protect neurons from a wide range of neurotoxic effects. Among all psychiatric medications, including

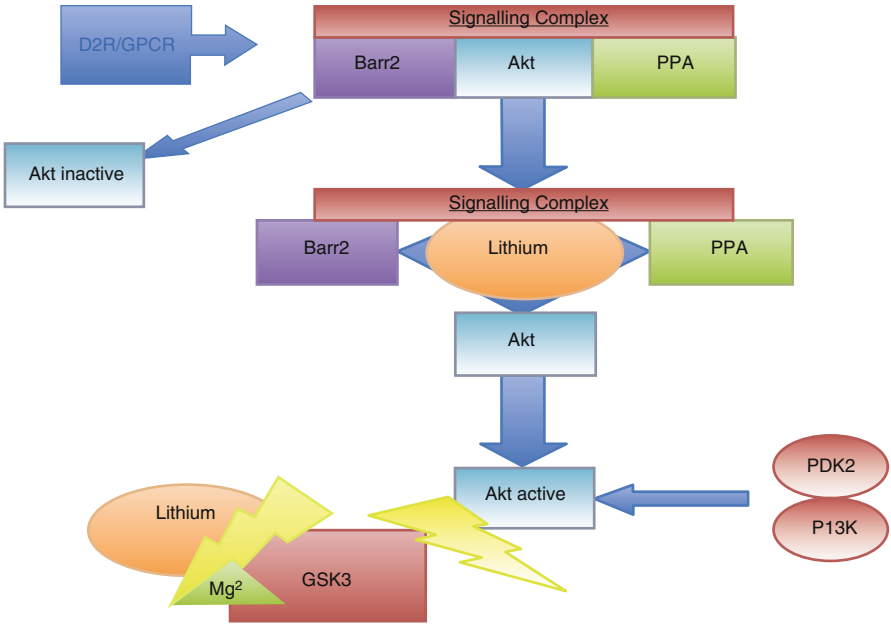

Fig. 4.4 Inhibition of glycogen synthase kinase-3 (GSK-3) by lithium (With permission reprinted from Brown and Tracy 2013). Lithium directly inhibits GSK-3 by competitive binding for magnesium (Mg^{2+}), disrupting the catalytic functioning of GSK-3. Lithium also indirectly inhibits GSK-3 by increasing serine phosphorylation, through P13K-mediated phosphorylation/activation of Akt. Lithium is able to activate Akt by disrupting the formation of a protein kinase B (Akt), beta-arrestin 2(βArr2), and protein phosphatase 2A (Akt;βArr2;PP2A)-comprised signaling complex, triggered by activation of the dopamine 2 receptor (D2R) and potentially other G-protein-coupled receptors (GPCR). The Akt;βArr2;PP2A signaling complex typically leads to inactivation of Akt, preventing GSK-3 inhibition; the destabilization of this signaling complex by lithium reduces Akt dephosphorylation, enhancing Akt activity, thus indirectly inhibiting GSK-3 (Brown and Tracy 2013)

antipsychotics, anticonvulsants, and antidepressants, lithium provides the most replicated evidence for neuroprotection in the widest range of neurodegenerative disease models (Lauterbach and Mendez 2011). The important question of whether lithium's intriguing pharmacodynamic properties really do translate into therapeutic neuroprotective effects in human subjects is discussed in detail in Chap. 9.

4.3.1 Effects on Neurotransmitters

The so-called monoamine neurotransmitters, which include dopamine, noradrenaline, and serotonin, are thought to play key roles in the modulation and control of emotion and cognition. Medications that interact with the effects of monoamines on their targets are used to treat psychiatric disorders such as mood disorders and schizophrenia. Lithium also exerts prominent and complex effects on several such

monoamine neurotransmitters. Upon ingestion, lithium becomes widely distributed in the central nervous system and interacts with a number of neurotransmitters (Juckel and Mavrogiorgou 2006).

Basic research has shown that lithium increases *serotonergic* neurotransmission via multiple mechanisms including increased synthesis of serotonin, increased uptake of tryptophan, and increased serotonin release (possibly by inhibiting presynaptic serotonin (5-HT_{1A}) receptors, with activation of postsynaptic 5-HT_{1A} and down-regulation of 5-HT_2 receptors (Manji et al. 1991)). Serotonergic effects of lithium have been suggested as being responsible for its anti-suicidal and anti-aggressive actions (Chap. 8) as well as contributing to antidepressant augmentation (Chap. 7).

With respect to the *dopamine* system, lithium administration does not seem to reduce basal dopaminergic tone, but it does inhibit increased dopaminergic activity. Chronic lithium has been reported to prevent haloperidol-induced dopamine receptor upregulation and to induce supersensitivity to dopamine applied iontophoretically (Gallager et al. 1978). Studies in animals and humans also reveal that lithium appears to block amphetamine-induced behavioral changes potentially mediated by dopaminergic neurotransmission (Huey et al. 1981).

With respect to the *glutamatergic system*, there is evidence that lithium competes with magnesium for binding to NMDA glutamate receptors (inhibitory action), increasing the glutamate availability in postsynaptic neurons. These effects of lithium on excitatory neurotransmitters (dopamine and glutamate) may be partially responsible for its antimanic, anti-suicidal, antidepressant, and antipsychotic effects, but further research is needed to fully understand how lithium works.

In contrast to its inhibitory effects on these excitatory transmitters, lithium increases *γ-aminobutyric acid (GABA)* neurotransmission, an inhibitory neurotransmitter that plays a crucial role in modulating both dopamine and glutamate neurotransmission, and through this action promotes the release of neuroprotective proteins and lowers levels of pro-apoptotic proteins (Malhi et al. 2013).

4.4 Pharmacogenetics of Lithium

Pharmacogenetics is a relatively new discipline in pharmacology that attempts to identify robust genetic biomarkers of medication responses. Such markers could serve as key elements to more precise, individualized medicines and offer the potential to improve treatment outcomes for patients. Naturalistic studies reveal that up to 20% of patients with bipolar disorder achieve complete remission while taking lithium. This group of patients has been referred to in the literature as "excellent lithium responders" (Grof et al. 1993). Lithium-responsive bipolar patients share distinct clinical features such as an episodic clinical course, no rapid cycling, and a family history of bipolar disorder. These features correspond to the "core phenotype" or "classic" bipolar I disorder (Chap. 5).

Previous studies have suggested that the lithium response is a strongly inheritable trait, but also one that varies considerably across individuals. Patients who respond well to lithium treatment might represent a relatively homogeneous

subtype of this genetically and phenotypically diverse disorder. Therefore, the search for genetic markers for lithium response in lithium responders has recently been intensified (Grof 2010). Several genome scans and meta-analyses have been completed (Perlis et al. 2009), but despite a significant genetic component for lithium-responsive bipolar disorder, pharmacogenetic studies have not yet produced replicated results or found biomarkers that would predict the outcome of lithium treatment. One possible explanation for the lack of conclusive pharmacogenetic findings is so far the varying definition of lithium response across studies (Alda 2015). Indeed, the assessment of lithium maintenance treatment response, and consequently the definition of the phenotype under study, is complicated by factors inherent to the natural history of bipolar disorder, since it is so variable and heterogeneous.

What offers some hope in this research area is the ongoing large international effort to elucidate the genetic underpinnings of lithium response in bipolar disorder. This effort is being coordinated by the Consortium on Lithium Genetics (Schulze et al. 2010) and has established the largest patient cohort to date for genome-wide association studies (GWAS) of lithium response, totaling over 2500 individuals. Clinical response to lithium was assessed using the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder (Manchia et al. 2013). The ConLiGen consortium recently presented genome-wide significant evidence of an association between lithium response and common genetic variants on chromosome 21: the genetic region associated with lithium response contains two genes for long, noncoding RNAs (lncRNAs), AL157359.3 and AL157359.4 (Hou et al. 2016). lncRNAs are increasingly appreciated as important regulators of gene expression, particularly in the brain. Confirmed biomarkers of lithium response would constitute an important step forward in the clinical management of bipolar disorder.

Another recent GWAS from Sweden and the United Kingdom was performed on over 2698 patients with subjectively defined (self-reported) lithium response and 1176 patients with objectively defined (clinically documented) lithium response and compared with a group of healthy controls (Song et al. 2015). When comparing lithium-responsive patients with controls, two imputed markers revealed genome-wide significant associations, one of which was validated in confirmatory genotyping. These two genetic markers are an intronic single nucleotide polymorphism (SNP) on chromosome 2q31.2 in gene SEC14 and spectrin domains 1 (SESTD1), which encodes a protein involved in regulating phospholipids (Song et al. 2015). Phospholipids have been strongly implicated as lithium treatment targets.

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Maintenance Treatment with Lithium

5

5.1 Introduction

Patients suffering from bipolar disorder experience an episodic illness with the risk of affective recurrences throughout most of their lives. Interepisodic subsyndromal mood symptoms and cognitive impairment may also occur in a proportion of patients with bipolar disorder. There is substantial intra- and interindividual variability in symptom severity, duration and number of episodes, degree of recovery between episodes, and the polarity pattern. Given the wide range of bipolar disorder's phenotypic expression, long-term treatment presents a major challenge for clinicians. Despite the availability of modern treatments, full, sustained recovery is difficult to achieve. By virtue of its recurrent nature and depending on the subtype of the disorder, patients have symptoms for approximately half of their lives, a finding that highlights the importance of optimizing long-term treatment and ameliorating affective symptomatology.

5.2 Goals of Maintenance and Long-Term Treatment

Due to the high, lifelong recurrence risk (for the majority of patients), pharmacological maintenance treatment of bipolar disorder is essential. The goals of long-term treatment are to prevent mood episodes (relapse during continuation treatment as well as recurrences during prophylactic treatment) (Fig. 5.1), prevent suicidal acts, reduce subthreshold symptoms, and enhance social and occupational functioning (Müller-Oerlinghausen et al. 2002). These are laudable goals, but sometimes difficult to achieve (Geddes and Miklowitz 2013). If episodes cannot be entirely prevented via prophylactic treatment, the secondary goal should be to at least reduce their frequency and severity. To attain these goals, long-term treatment is vitally important in the management of bipolar disorder. Well-planned and conducted long-term pharmacological treatment can be highly effective in achieving these goals,

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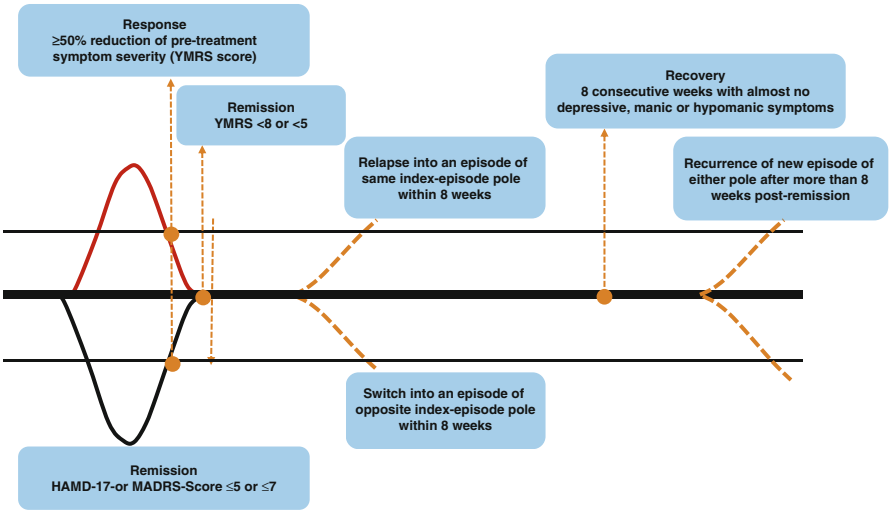

Fig. 5.1 Nomenclature of course and outcome in bipolar disorder (The International Society for Bipolar Disorders Task Force; Tohen et al. 2009). *HAMD-17* Hamilton Depression Rating Scale-17 items, *MADRS* Montgomery–Åsberg Depression Rating Scale, *YMRS* Young Mania Rating Scale

especially when combined with psychoeducational forms of psychotherapy (Miklowitz and Gitlin 2014).

The prevention of future mood episodes is called maintenance or prophylactic (preventive) treatment. By definition, it follows continuation treatment for either mania or hypomania or depression. Again by definition, continuation follows the acute treatment phase of any mood episode. The main goal of acute phase treatment is to alleviate symptoms to the point of remission (Tohen et al. 2009; Fig. 5.1). Once remission is achieved, the goals of continuation treatment are to protect patients from the reemergence of their symptoms, i.e., relapses, and from treatment-emergent affective switches (TEAS), defined as an episode of opposite polarity within the continuation phase (Grunze et al. 2013). Unfortunately, there is no precise definition as to when continuation treatment evolves into the maintenance treatment phase. Roughly speaking, once a patient is stable for 3–6 months after effective treatment of an episode, further treatment is considered maintenance therapy.

5.3 When Should Maintenance Treatment Be Started?

The question of when to begin prophylactic, long-term treatment is extremely important to patients and physicians for obvious reasons. The decision depends on the assessment of recurrence risk and the psychosocial impact of recurrences as assessed by patient and the family. The acceptance of long-term treatment by many patients is relatively low in the early stages of the disorder. Since bipolar disorder typically emerges in adolescence and early adulthood (mostly at ages 15–25), it is

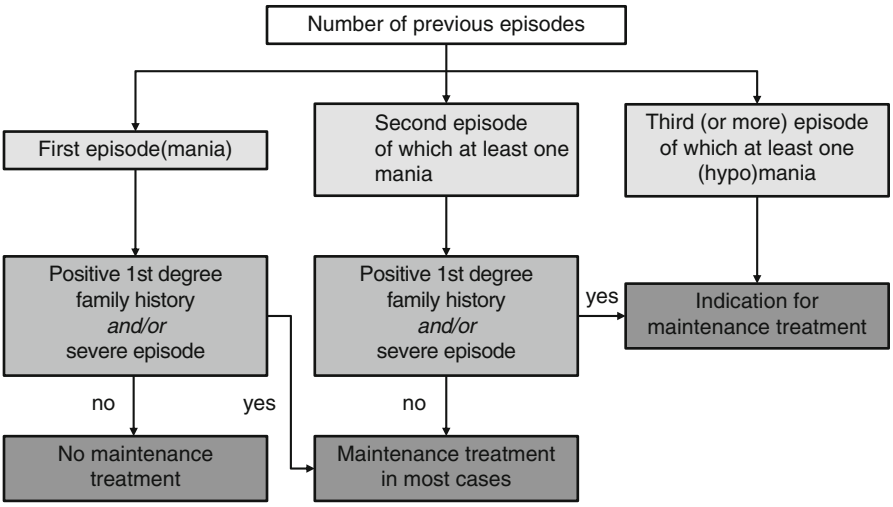

Fig. 5.2 Algorithm of maintenance treatment indications (Adapted from Dutch guidelines; Nolen et al. 2008)

often understandably quite difficult to convince patients of the need for daily—or even lifelong—medication treatment at a time in their lives when a primary developmental goal is independence from their parents. Unfortunately, taking medication often symbolizes a dependency on outside forces and interferes with emerging feelings of autonomy.

There is no clear consensus on the question of when to start, but a pragmatic approach is to initiate treatment as soon as possible once the diagnosis of bipolar disorder has been established. This requires at least one depressive and one (hypo-) manic episode according to the standard classification systems. Some practice guidelines recommend that maintenance treatment starts after the first manic episode. Representing a compromise between various expert opinions and guideline recommendations, the Dutch guidelines consider the number of episodes and other relevant clinical variables such as severity and a positive family history of bipolar disorder suggestive of an increased genetic risk (Fig. 5.2; Nolen et al. 2008). Thus, if the first manic episode is severe, and there is a family history, they recommend considering the start of maintenance treatment. Otherwise, with two episodes (one of them manic), maintenance treatment should be initiated if at least one is of particular severity or the patient has a positive family history (Nolen et al. 2008).

There is evidence that lithium's prophylactic efficacy may decrease with a longer delay between the onset of illness and initiation of treatment (Franchini et al. 1999). In contrast, two large cohort studies found that a treatment latency (delay of treatment initiation) of even several years (7–10 years) did not negatively influence the prophylactic outcome with lithium (Baldessarini et al. 2003; Baethge et al. 2003).

5.4 Pharmacological Maintenance Treatment in Mood Disorders

The mainstays of maintenance pharmacotherapy are mood stabilizers. The term mood stabilizer is widely used in the context of treating bipolar disorder, but the US Food and Drug Administration (FDA) does not officially recognize the term, and there is no consensus among investigators or clinicians on its definition. Pragmatically, the definition of an optimal medication that would qualify as a mood stabilizer would be an agent that demonstrates efficacy in treating acute manic and depressive symptoms while preventing future manic and depressive episodes (Bauer and Mitchner 2004). Today, there is consensus that the group of mood stabilizers consists of lithium salts; the anticonvulsants carbamazepine, valproate, and lamotrigine; and some of the atypical antipsychotics (for a discussion of anticonvulsants and atypical antipsychotics as mood stabilizers, see Chap. 13).

5.5 Maintenance Treatment of Bipolar Disorder with Lithium

5.5.1 Initial Evidence and Landmark Studies

After Cade's groundbreaking discovery in 1949 demonstrating that lithium triggers prominent acute antimanic activity, in the mid-1950s in Risskov, Denmark, Schou administered lithium to the first bipolar patients on a longer-term basis and noted that patients suffered fewer manias and depressions since beginning to take lithium (Schou 1956). His observations and positive single-patient case observations from other European countries led the Danish physicians Baastrup and Schou to conduct the first prospective longitudinal trial that included patients with frequent recurrences of bipolar disorder or depressive disorder (Baastrup and Schou 1967). This naturalistic study demonstrated that recurrences were less frequent and severe during long-term lithium treatment than before lithium was given. Some but not all patients even remitted fully. Stimulated by these first positive results, the Danish physicians joined forces with other European researchers and expanded the number of lithium-treated patients, publishing later a large prospective follow-up study of 250 patients, again revealing effective recurrence prevention (Angst et al. 1970). The first lithium study that introduced placebo to demonstrate lithium's efficacy was a so-called discontinuation trial: all subjects in the study had been taking lithium long term before entering the trial; a significant number relapsed shortly after receiving the placebo instead of lithium (Baastrup et al. 1970).

The results of these landmark studies spurred the prescription of lithium in the long-term treatment of patients with mood disorders in many countries in and outside Europe. The Baastrup trial from 1970 had a tremendous influence on the treatment of bipolar disorder and on patients' lives: for the first time, a specific treatment was available to help patients with bipolar disorder. For many years

(until the late 1980s when carbamazepine was introduced), lithium was the only available treatment with any demonstrated efficacy in the prophylactic treatment of bipolar disorder.

5.5.2 Growing Evidence for Lithium's Efficacy from Randomized Trials

Starting in the early 1970s, its efficacy in preventing mood episodes in bipolar disorder was demonstrated in several randomized placebo-controlled studies (Coppen et al. 1973; Prien et al. 1973). Lately, new evidence has emerged from large trials conducted primarily to investigate the efficacy of newer agents compared with placebo, but which also included a lithium arm as an active comparator (Goodwin and Geddes 2003). Across a series of randomized placebo-controlled studies and several meta-analyses, lithium has proven to be effective in the long-term treatment of bipolar disorder, specifically in preventing mood episodes better than placebo. While some initial analyses from heterogeneous populations seemed to indicate less robust efficacy in preventing depressive episodes (Geddes et al. 2004), a more recent study, which was added to the pool of controlled data, also revealed solid efficacy in preventing depression (Weisler et al. 2011).

5.5.3 The Recent Evidence from Meta-analyses

In the past decade, at least three systematic reviews and meta-analyses, each with somewhat different analytic approaches and inclusion criteria, have uniformly confirmed lithium's efficacy in preventing relapses of bipolar disorder (Geddes et al. 2004; Miura et al. 2014; Severus et al. 2014).

The systematic review and meta-analysis by Geddes et al. (2004) evaluated the efficacy and acceptability of lithium for relapse prevention in bipolar disorder. Their meta-analysis of five placebo-controlled lithium maintenance trials (including 770 participants) showed that lithium reduces the risk of manic relapses by 38 % and depressive relapse by 28 %; the relative risk (RR) was 0.65 and the number needed to treat (NNT) was 5. Lithium demonstrated a statistically significant benefit over placebo in preventing manic episodes, but no statistically significant benefit over placebo in preventing depressive episodes (Geddes et al. 2004).

Since then, the evidence base has grown substantially, particularly through lithium's use as an active comparator in pivotal trials of new medications. In the latest meta-analysis, the data were analyzed comparing lithium with placebo and other treatments regarding dropouts for reasons other than a mood episode and study completion (no mood episode and no dropout for reasons other than a mood episode) (Severus et al. 2014). Seven trials with a total number of 1580 participants were included in comparing lithium with placebo. Lithium was more effective than placebo in preventing overall mood episodes (random effects RR = 0.66), manic episodes (random effects RR = 0.52), and, dependent on the type of analyses applied,

depressive episodes (random effects RR = 0.78, fixed effect RR = 0.73). Lithium was inferior to placebo in leading to dropouts for reasons other than a mood episode, but superior to placebo in terms of study completion (random effects RR = 1.69). Seven trials were included ($n = 1305$) comparing lithium with anticonvulsants. In preventing manic episodes, lithium exhibited superiority to anticonvulsants (random effects RR ≡ 0.66). However, there was no significant difference in the prevention of overall mood episodes, depressive episodes, dropping out for reasons other than a mood episode, or study completion (Severus et al. 2014).

A recent *network meta-analysis* investigated the comparative efficacy and tolerability of available pharmacological treatment strategies for bipolar disorder (Miura et al. 2014). All randomized controlled trials published before June, 2013 were included that compared active treatments for bipolar disorder (or placebo), either as monotherapy or as add-on treatment, for at least 12 weeks. Primary outcomes were the number of participants suffering a recurrence of any mood episode and the number of participants who discontinued the trial because of adverse events. The authors assessed efficacy and tolerability data from 33 randomized controlled trials published between 1970 and 2012 that examined 17 treatments for bipolar disorder (or placebo) in 6846 participants. Although most of the drugs analyzed were more efficacious than placebo and generally well tolerated, the authors concluded that differences in the quality of evidence and the side effect profiles should be taken into consideration by clinicians and patients. In view of its efficacy in preventing both manic episode and depressive episode relapse or recurrence and the better quality of the supporting evidence, the authors concluded that lithium should remain the first-line treatment when prescribing a relapse prevention drug in patients with bipolar disorder, notwithstanding its tolerability profile (Miura et al. 2014).

5.5.4 Predicting the Response to Lithium: How to Select the "Right" Person for Lithium Treatment?

Many patients with bipolar disorder can be stabilized very effectively with lithium maintenance if their lithium-responsive clinical profile is correctly identified, and they are adequately treated and monitored (Grof 2006; Gershon et al. 2009). These patients usually respond well to lithium when acutely ill, yet benefit from it most strikingly in long-term treatment. Specific investigations of so-called excellent responders to lithium in long-term prophylaxis have deepened our understanding by clarifying the factors that characterize those patients who, despite a previous history of intense illness, remain completely well for years on adequate lithium treatment. The distinct features of these patients are captured in their clinical course, family history, comorbidity profile, psychopathology, and early development. These characteristics are vital to identify those patients for whom long-term lithium stabilization should definitely be the treatment of first choice.

Patients who do best on lithium are those who demonstrate the so-called classic profile of bipolar disorder. The features corresponding to the classic profile are listed in Table 5.1. Lithium's advantages are manifested in both the treatment

Table 5.1 Clinical features linked to good response to lithium

Discrete episodes with typical symptom cluster
Family history of bipolar disorder
Family history of lithium response
Full remission between episodes
Lack of mood-incongruent psychotic features

outcome and tolerability. These excellent responders also tolerate lithium quite well with relatively few side effects. The striking well-being of lithium responders stands out over time, and they frequently decompensate when switched to other mood stabilizer classes (Grof 2006).

Clinical features that predict *poorer* outcome with lithium include patients with mixed or dysphoric mania, rapid cycling (see below), mania with psychotic features, negative family history of mood disorders in first-degree relatives, occurrence of comorbid substance and alcohol dependency, and an illness pattern revealing an immediate switch from depression into mania. In addition, several investigators have described an association between the presence of bipolar disorder's "atypical features" and the quality of response to lithium. Other features predicting a poorer prophylactic response to lithium include incomplete remission between episodes and mood-incongruent psychotic symptoms. As an example of these predictors, in a naturalistic long-term study of 336 patients with bipolar I and II disorder (among them were patients undergoing lithium treatment for up to 30 years), the risk for recurrence was negatively influenced by the presence of atypical features, mainly by mood-incongruent psychotic symptoms, interepisodic residual symptomatology, rapid cycling, and a family history of non-episodic psychiatric disorder (Pfennig et al. 2010).

Overall, lithium's efficacy (and that of other mood stabilizers) has rarely been analyzed specifically in *bipolar type II disorder*. No clear difference was detected in naturalistic studies comparing efficacy between bipolar type I and II disorder (Tondo et al. 1998).

Possible *gender differences* in the response to lithium also remain poorly studied. In the only published study of 360 bipolar patients, contrary to the authors' prediction, women displayed slightly (but not significantly) superior responses to lithium maintenance therapy (Viguera et al. 2001).

5.5.5 Lithium in Offspring of Bipolar Parents

Duffy and colleagues carried out systematic prospective studies of the offspring of lithium responders and nonresponders. Their major findings include the observation that, despite a genetic risk for bipolar disorder, these offspring manifest a broad range of psychopathology (Duffy et al. 2014). Their research also showed that the children of adult lithium responders present, like their parents, with a recurrent remitting course. Preliminary evidence from case series supports the hypothesis that some youths at risk for bipolar disorder demonstrate early

psychiatric disturbances and bipolar parents' offspring with manifest bipolar disorder may themselves benefit from lithium, especially when their parents responded well to it (Duffy 2006).

5.5.6 Lithium in Rapid Cycling

The term "rapid cycling" was introduced by Dunner and Fieve in 1974 to denote a course of illness in which four or more mood episodes occurred in the year preceding their study of lithium long-term therapy. For many years, rapid cycling was considered a predictor of poor response to lithium, and, in the narrowest sense, this statement is true. However, more recent studies have shown that rapid cycling predicts a poor response to any and all mood stabilizer monotherapies. Tondo et al. (2003) analyzed 16 studies addressing the effects of rapid cycling and treatment choice on clinical outcome in bipolar disorder. Patients (905 with rapid cycling, 951 without) were treated with carbamazepine, lamotrigine, lithium, topiramate, or valproate, alone or with other agents, over an average of about 4 years. Although only lithium and carbamazepine were directly compared in patients with rapid cycling, pooled recurrence rates and non-improvement rates did not suggest that any specific treatment was superior to any other. Instead, rapid cycling was associated with less effectiveness of all the treatments evaluated (Tondo et al. 2003). A more recent randomized double-blind study comparing divalproex (valproate) and lithium in the long-term treatment of rapid cycling bipolar disorder confirmed this finding: relapse rates were 51 % in those on divalproex compared to 56 % in those on lithium, and in both groups, 22 % of patients relapsed into manic or mixed states. Also, no statistically significant differences were observed between treatment groups in premature discontinuation due to side effects, median time to treat emerging symptoms of any type of episode, or median survival in the study (Calabrese et al. 2005).

In summary, decades after the introduction of the term "rapid cycling," it is evident that the generally observed relative lack of efficacy appears in conjunction with all standard pharmacological treatments, not just with lithium (Bauer et al. 2008).

5.5.7 Discontinuing Lithium Long-Term Treatment

The abrupt (within days or few weeks) discontinuation of prophylactic treatment in bipolar disorder carries the high risk of a sudden mood recurrence—especially mania—within several months, even after several years of stability (Suppes et al. 1991; Baldessarini et al. 1999). Even a sharp reduction in dose may carry some risk (Suppes et al. 1993). A rapid discontinuation of long-term treatment in patients with bipolar disorder happens frequently in clinical practice. Reasons for interrupting treatment may be (a) adverse treatment effects, (b) pregnancy, (c) patients' unwillingness to continue treatment following prolonged well-being or relatively minor side effects, (d) patient's nonadherence to recommended treatment, (e) clinician dissatisfaction with response ("unresponsiveness") and

electing to try alternative treatments and (f) during controlled therapeutic trials involving switching from lithium to placebo or alternative active treatments (Baldessarini et al. 2006).

The phenomenon of the discontinuation-associated risk of early recurrence of major mood episodes has important clinical implications. These include the need to evaluate safer methods of interrupting long-term maintenance treatment, particularly when clinical indications for rapid cessation are compelling and gradual discontinuation is not feasible (Suppes et al. 1993). Most importantly, patients must be informed about the risks and implications of stopping their long-term treatment. If lithium is gradually discontinued, the risk of early recurrences, particularly of mania, is lower. After discontinuation because of "unresponsiveness," the patient and physician often realize that the lithium medication was, in fact, at least partly effective when the patient experiences a recurrence after having stopped prophylaxis.

There is clinical experience that if discontinuation becomes necessary, lithium should be discontinued gradually whenever possible. The general recommendation is to taper the lithium dose over a period of weeks, or preferably months, and to monitor carefully for any signs indicating a new episode. It remains unclear whether these same caveats apply if the bipolar patient is also taking another mood stabilizer. In the absence of evidence, it is prudent to taper lithium whenever possible, even if other mood stabilizers are being prescribed.

There is limited evidence that a rebound might not arise in patients with a classical course of bipolar disorder who experience full remission between episodes and present only mood-congruent symptoms during acute episodes (Baldessarini et al. 2006). Discontinuing other mood-stabilizing drugs might cause similar reactions; however, comparable studies are still lacking. The suicide risk also rises when long-term treatment is interrupted.

5.5.8 Does Lithium Treatment Lose Efficacy over Time in Long-Term Treatment?

Response rates in early controlled, long-term studies of lithium ranged from 70 to 80 % in the 1960s and 1970s. During the next few decades, however, these high response rates could not always be replicated in clinical practice, and physicians began to wonder whether lithium was still the best treatment option. The observed drop in response rates was probably a result of the widespread use of lithium in less controlled settings and of the introduction of modern diagnostic systems that broadened the criteria of bipolar disorder in the 1990s. Along with the need to distinguish the efficacy of various specific pharmacological treatments, it is essential to distinguish subtypes of bipolar disorder to achieve maximum response in long-term treatment. A substantial number of patients with bipolar disorder also have psychiatric comorbidities such as substance abuse, psychotic features, and medication-induced rapid cycling and therefore deviate considerably from the original manifestation of manic-depressive illness.

Lithium remains the first choice for the maintenance treatment of patients with bipolar disorder who display a classical course of illness without mood-incongruent psychotic features and with no psychiatric comorbidity. Several naturalistic long-term studies (more than 10 years of lithium treatment) from different countries indicate that lithium's prophylactic efficacy does not decrease over time in the vast majority of bipolar patients (Rybakowski et al. 2001; Baldessarini and Tondo 2000; Berghöfer et al. 2008). In one of the largest long-term studies, 346 patients with bipolar disorder I or II were followed for up to 20 years (mean period of 10.0 years). The "morbidity index," an established outcome measure for research in mood disorders that includes severity and length of episodes, did not change significantly during the observation period, suggesting that the long-term response to lithium maintenance therapy remains stable over time (Berghöfer et al. 2013).

5.5.9 Does Lithium Treatment Lose Efficacy After Treatment Discontinuation?

Anecdotal reports and observational studies in the 1980s and 1990s have suggested that long-term lithium treatment may lose efficacy (Post et al. 1992; Maj et al. 1995). Since then, this is an ongoing controversy. In describing patients who responded well during the initial years of lithium prophylaxis, the term "loss of efficacy" has been used in two different contexts: First, the *loss of efficacy over time*, i.e., during the initial years of lithium administration, the patient remains well but later manic or depressive episodes reappear, although lithium treatment had not been discontinued. For example, in a naturalistic setting, Maj and co-workers in Italy analyzed the course of illness in 43 bipolar patients who had been successfully treated with lithium for 2 years: during a 5-year follow-up period, a substantial number of patients experienced recurrences despite their having been initially classified as responders to prophylactic lithium treatment (Maj et al. 1989). Second, the *loss of efficacy after discontinuation*, meaning that during the initial years of lithium treatment, the patient was doing well; however, the recurrences reappear after discontinuation, and lithium's reinstitution is then ineffective in preventing mood episodes (Post et al. 1992). Some authors described the latter phenomenon "lithium-discontinuation-induced refractoriness" (despite adequate lithium serum levels; Bauer 1994) and note that nonresponse to reinstituted lithium maintenance should be considered among possible risks associated with interrupting effective lithium prophylaxis (Maj et al. 1995; Tondo et al. 1997). Other authors conclude from their analyses of bipolar patients' life charts that this phenomenon appears to be very rare and may be caused by inappropriate patient selection for long-term lithium treatment (Berghöfer et al. 1996). The most recent and comprehensive review (including a meta-analysis of three studies) yielded no convincing evidence that lithium is less effective when treatment is discontinued and restarted, compared to uninterrupted treatment phases (de Vries et al. 2013). In summary, the phenomenon of efficacy loss after interruption and reinstitution of lithium therapy seems to occur infrequently.

5.5.10 Position of Lithium for Maintenance Treatment in Guidelines

In an effort to improve quality and cost-effectiveness, medical associations, insurance companies, and even some governments have promoted the implementation into everyday practice of guidelines for both general practitioners and specialists (Morris 2015). Guidelines are intended to assist the practitioner with routine decision-making and be based on the best available evidence. Experts or professional associations usually write these guidelines, but they are also subjected to criticism because of having been collated from highly heterogeneous findings (Grof and Müller-Oerlinghausen 2013).

Specialists' associations have issued many guidelines for bipolar disorder during the past decade (e.g., American Psychiatric Association [APA], Canadian Network for Mood and Anxiety Treatments [CANMAT], Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde [DGPPN]), and other national institutions (e.g., National Institute for Clinical Excellence [NICE], Scottish Intercollegiate Guidelines Network [SIGN]) and international organizations (e.g., World Federation of Societies of Biological Psychiatry [WFSBP]). There is widespread agreement on the role of lithium in bipolar disorder across these many national and international treatment guidelines: lithium plays a very prominent role in the latest guidelines on the prophylactic, long-term management of bipolar disorder and is considered the first-choice treatment ("gold standard"). For bipolar maintenance, the evidence is overwhelming in support of lithium and very thin for valproate and carbamazepine. Newer agents may increase our armamentarium to some extent, but it is unclear whether they represent a major advance in treatment. They still need to be tested against the gold standard, lithium.

However, some areas of divergence regarding lithium's role among the guidelines do exist, including its anti-suicidal and prophylactic effect in unipolar depression and the prophylaxis of specific subtypes of bipolar disorder. In the "real therapeutic world," both individual clinical issues and differing prescribing rationales may result in the use of alternative agents, especially for long-term prophylaxis. For example, in contrast to the use of lithium in acute classical mania, the lack of consensus on the choice of a prophylactic agent for subtypes of bipolar disorder may reflect a shortage of adequate evidence to enable multiple international guideline committees to reach homogeneous conclusions (Crossley et al. 2006).

5.6 Lithium Maintenance Treatment of Recurrent Unipolar Depression

Since its discovery in modern psychiatry in 1949, lithium has been mainly considered as a prophylactic treatment for bipolar disorders and as an acute treatment for mania. The potential value of lithium in preventing depressive episodes in patients with recurrent unipolar depression has received less attention. However, its prophylactic properties have been investigated since the late 1950s in both bipolar *and* unipolar depressive disorders.

Because the controlled studies on lithium as a preventive treatment in recurrent depression are at least 30 years old, most of the methodologies—from methods of blindness to varied definitions of relapse (e.g., hospitalization vs. change in symptom rating scales) to shifting diagnostic definitions—do not reflect current standards. Despite this, lithium has exhibited consistent evidence of its ability to prevent depressive episodes in unipolar depression (Souza and Goodwin 1991). The latest comprehensive review and meta-analysis by Davis (2006) included nine randomized, double-blind, placebo-controlled studies in recurrent unipolar disorder and found that lithium was highly effective: 75 % of patients suffered a recurrence on placebo versus 36 % on maintenance lithium (corresponding to a 39 % decrease in relapses; odds ratio = 0.18). It is noteworthy that this efficacy in unipolar recurrent depression is similar to lithium's prophylactic efficacy in bipolar disorder (Davis 2006). A meta-analysis of another method of examining relapse prevention—"mirror-image" studies—in which relapse rates on lithium are compared to those pre-lithium, also demonstrated efficacy with a reduction in relapse frequency by 69 % (effect size = 0.72) (Davis 2006).

Despite these relatively convincing findings, lithium is infrequently employed as a primary preventive treatment for unipolar depression in the United States. As an example, in the American Psychiatric Association practice guidelines for major depressive disorder, lithium is not even mentioned in the section on maintenance treatment, surprisingly. In contrast, lithium is prescribed in most European countries for this indication quite regularly, and some international guidelines recommend lithium as a major alternative to antidepressants (World Federation of Societies of Biological Psychiatry, Bauer et al. 2015). As a consequence, lithium should be considered early in the algorithm of treatment for those patients who suffer highly recurrent, discretely episodic depressions (with interepisodic remission in contrast to those with more chronic depressive symptomatology).

5.7 How Can Lithium Maintenance Treatment Be Optimized?

Patients with bipolar disorder who fail to respond sufficiently or do not tolerate prophylactic monotherapy with lithium well should be candidates for switching to a different mood stabilizer or for adding a second mood stabilizer (e.g., an anticonvulsant; Baethge et al. 2005) to lithium treatment (see also Chap. 13). The question of whether switching vs. adding should be recommended first in such cases cannot be satisfactorily answered from the available database. Little controlled data exists to help guide physicians in choosing whether to replace one monotherapy with another or when to add a second drug, but adding a second mood stabilizer rather than switching to a different drug seems to be the method of choice in most cases. It is worth trying on an individual basis, but there is no conclusive evidence so far that a combination improves the outcome significantly. Before initiating combination treatment, the clinician should first consider optimizing prophylactic monotherapy (Table 5.2).

Table 5.2 Methods to improve outcome in partial and nonresponders to lithium maintenance

Verify diagnosis "bipolar disorder" with respect to subtypes and specifiers of illness (e.g., rapid cycling, seasonal pattern, psychotic features)
Check compliance more frequently (measure lithium blood level)
Treat psychiatric comorbidity (e.g., substance dependency)
Increase serum levels of lithium to upper limit (1.0 mmol/L, if tolerability allows)
Discontinue drugs that may induce rapid cycling (tricyclics, psychostimulants)
Exclude occult somatic illness (e.g., endocrine dysfunctions, neurological and autoimmune diseases)
Add low dose levothyroxine (L-T4, 50–150 mcg/d) if basal TSH is elevated (subclinical hypothyroidism, 4.0–4.5 mU/L, depending on the laboratory)
Install appropriate systematic life chart methodology (graphical reconstruction of previous course of illness and medication)

It is obvious that treatment intolerance secondary to side effects left untreated will lead to poor treatment compliance. Other factors frequently leading to noncompliance are patients' illness concepts and treatment expectations that differ from those of the treating physician. Knowledge about a medication and its effects may play an important role in establishing compliance in long-term treatment. The lack of sufficient information on an illness course and treatment may be resolved by restating instructions and using educational programs on a regular repeated basis (e.g., once a year to refresh one's knowledge of the best practice of lithium therapy) (Schaub et al. 2001). Recommendations of suitable information sources (e.g., easy to understand lithium brochures or serious internet sources; Monteith et al. 2013) help patients and their relatives to better understand bipolar disorder and enhance treatment compliance. Patient education about lithium treatment should be intensified in elderly patients taking lithium because adverse drug reactions pose a greater risk to the elderly. More details on practical issues related to long-term treatment with lithium are found in Chap. 11.

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Treatment of Mania with Lithium

6

6.1 Introduction

Lithium's efficacy in acute mania has the longest history of any of its therapeutic uses. The first report of lithium's efficacy was the now legendary report by Cade of his treatment of ten chronic and episodically manic patients with lithium (Cade 1949; for more details see Chap. 3). Over time, especially over the last 20 years, more and better studies were published. This trend was enhanced by the need for systematic data on the antimanic effects of other potential agents. Since lithium had already been established as the gold standard treatment for acute mania, a number of these studies employed lithium as an active comparator, thus increasing the number of well-designed studies that examined lithium's efficacy for acute mania (even though the goal of these studies was to evaluate the efficacy of the other medications). As an example, the first acute mania trial evaluating lithium's efficacy using modern methodology was published in 1994 in which lithium was used as an active comparator to valproate in a three-arm double-blind study designed to test valproate's efficacy (Bowden et al. 1994).

6.2 Lithium as an Antimanic Medication: Recent Studies

Recent studies have validated what Cade and Schou independently described decades ago: lithium is an effective antimanic agent that does not rely upon sedation for its efficacy. Most modern lithium studies in this area have been active comparator studies, only some of which have also employed a placebo control. Of the 18 randomized double-blind lithium trials that have been published, only seven also used a placebo control. The relative lack of placebo-controlled studies is understandable given the clinical and ethical difficulties in treating significant numbers of acutely manic hospitalized patients with placebo.

In these modern studies, the usual outcome measure is response at 3 weeks, with response typically defined by a 50 % reduction in manic symptoms using a

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validated, reliable rating scale such as the Young Mania Rating Scale (YMRS). Certainly, a 50 % improvement is easily observable and clinically relevant. Nonetheless, a manic patient who is only 50 % better may still be rather symptomatic. Remission rates, defined typically as a YMRS rating of <12, are, of course, often substantially lower than response rates after 3 weeks of treatment and are not reported in all acute mania studies. Across studies, response rates to lithium over the typical 3-week trial for acute mania average 50 % compared to placebo response rates of 25 %, a significant and clinically highly relevant difference. Another measure of efficacy is the number to treat (NNT) which is defined as the number of patients that need to be treated to yield one additional responder compared to placebo. For acute mania, lithium's NNT is 4, indicating a robust clinical effect (Srivastava and Ketter 2011).

As noted, more commonly, lithium's efficacy in this area has been compared to (other than placebo) anticonvulsants such as valproate and carbamazepine, first-generation antipsychotics (FGAs) such as haloperidol, and second-generation antipsychotics (SGAs) such as risperidone, olanzapine, quetiapine, and aripiprazole. Overall, lithium is as effective as the antipsychotics, albeit with a somewhat slower onset of efficacy. At least one study found lithium to be more effective than carbamazepine (Lerer et al. 1987). In a placebo-controlled study, lithium and valproate were equally effective in treating acute mania with both active treatments significantly more effective than placebo (Bowden et al. 1994). In this study, valproate was somewhat better tolerated than lithium as measured by premature termination rates for intolerance.

No other antimanic agent has a lower (therefore demonstrating greater efficacy) NNT than lithium, although a few—risperidone and carbamazepine—also exhibit NNTs of 4 (Srivastava and Ketter 2011).

6.3 Combination Studies with Lithium for Acute Mania

The response to lithium as defined by a 50 % improvement, achieved by only 50 % of treated patients, leaves much to be desired, especially since 50 % improvement in manic symptoms would still leave the individual significantly symptomatically impaired. (This efficacy rate is not different from what is seen in studies with all other antimanic medications.) Another corollary of this observation is that 3 weeks is simply not long enough for an antimanic medication to work fully. Because the efficacy of all the individual agents is better than placebo but, most of the time, not good enough and in order to increase both the number of responders and the quality of response, the strategy of combination therapy for acute mania has become more common in clinical practice and is now supported by a database of well-controlled studies. The hope/assumption is that two antimanic agents prescribed in combination would be more effective than either agent alone.

Combination studies involving lithium have used two designs. The most common type of study evaluates the efficacy of lithium or valproate with the addition of either an SGA or placebo, thus testing the additive efficacy of the antipsychotic.

A smaller number of studies ($n = 3$) have tested the efficacy of the addition of lithium to an antipsychotic compared to the antipsychotic alone (Ogawa et al. 2014).

Overall, adding an antipsychotic to a more classic mood stabilizer such as lithium or valproate yields significant benefit in both response and remission ($p < .0001$). In general, the addition of an antipsychotic is associated with a 20–25 % increase in mania responses compared to the classic mood stabilizer alone. There is no consistent evidence that any one antipsychotic shows more robust effect in combination with lithium or valproate compared to any other.

Combination studies in which the additive effect of lithium to an antipsychotic was tested showed similar significant benefit ($p < .0001$). This was driven mostly by a large ($n = 356$) recent study in which the additive efficacy of lithium to quetiapine for acute mania was evaluated (Bourin et al. 2014). Mania rating change scores, response rates, and remission rates all demonstrated greater improvement in the lithium/quetiapine group compared to the quetiapine/placebo group. Higher lithium levels (>0.6 mEq/L) were associated with a more robust response.

Not surprisingly, compared to those treated with monotherapy for acute mania, subjects on combination therapy experience a higher side effect burden such as weight gain and sedation. Extrapyramidal symptoms were more common in some but not all studies. Similarly, dropout rates were more common in combination treatment in only some studies.

6.4 Meta-analyses of Antimanic Agents and Lithium

Using the information just described, two meta-analyses compared the efficacy of all antimanic agents tested in controlled studies for at least 3 weeks (Cipriani et al. 2011; Yildiz et al. 2011). Because of slight differences in inclusion and exclusion criteria, results across the two meta-analyses were very similar, but not identical. Evaluating efficacy, lithium was more effective than placebo and was in the middle of the group of all antimanic agents as measured by effect size (0.37 and 0.39, respectively, in the two meta-analyses) or odds ratio. Lithium showed somewhat lower acceptability ratings compared to some other antimanic agents, as measured by treatment discontinuation. However, this measure of acceptability does not take into account other factors usually included in acceptability such as side effect burden, toxic effects, long-term health issues, and so forth. In one of the meta-analyses (Yildiz et al. 2011), the faster efficacy of antipsychotics compared to lithium was demonstrated.

6.5 Predictors of Response to Lithium for Acute Mania

When Cade did his early work, the relevant question was whether lithium had specific efficacy in mania vs. other diagnostic groups such as schizophrenia. Since then, the establishment of reliable predictors of treatment response has become

Table 6.1 Predictors of response to lithium in acute mania

Lower levels of agitation/hyperactivity
Euphoric, grandiose features (lack of depressive or mixed features)
<10 lifetime manic episodes
Past history of response to lithium in acute mania
Lack of rapid cycling history

more sophisticated and includes clinical and demographic factors. Response predictors achieve even more importance when, as now, in treating acute mania, there are so many choices available. Table 6.1 summarizes our knowledge on predictors of response to lithium in treating acute mania.

As noted above, earlier studies described a poorer response to lithium (relative to sedating antipsychotics) in manic patients with high levels of overactivity/agitation. Whether this reflects a truly differential response to the two agents or the usefulness of sedation in behavioral control of manic patients is less clear. It is well established, however, that psychotic thinking per se is not a differential predictor of lithium's antimanic efficacy, compared to valproate and probably to antipsychotics. As an example, quetiapine at a mean dose of almost 600 mg in responders did not show greater efficacy in psychosis measures compared to lithium in a double-blind, acute mania study (Bowden et al. 2005). Depressive symptoms within a manic episode, i.e., mixed mania, seem to respond less well to lithium compared to valproate (Bowden et al. 1994). Finally, one study found that greater number of prior episodes (beyond ten episodes) predicted a poorer response to lithium (Swann et al. 1999). Rapid cycling may also predict a poorer response to lithium in acute mania.

Of course, beyond the data just noted above, common sense predictors (sometimes validated by data) that should guide treatment response include a past history of response and side effect profile. Additionally, patient preference should always be taken into account since it will predict treatment adherence during maintenance treatment. Finally, although it is always possible to switch medications after the resolution of an acute episode and the beginning of longer-term maintenance treatment, the idea of starting a medication that will be continuous during the acute and maintenance phases has an inherent appeal. Lithium certainly fits that description for many bipolar patients.

In choosing a specific antimanic agent, the only medical contraindications to lithium would be markedly impaired renal function and acute myocardial infarction. In this circumstance, any other agent would be preferable.

Earlier case series suggested the possibility that patients who discontinued lithium and then became manic were less likely to respond to lithium during this second trial. Subsequent study using a less selected population suggested that, although this happened occasionally, generally, bipolar patients respond well to lithium as an acute antimanic agent when re-treated (Coryell et al. 1998).

6.6 Lithium as a Treatment for Hypomania

With the recognition of bipolar II disorder as a distinct subtype of manic-depressive illness with its hypomanias and depressions and no history of manias, the question of the optimal treatment of acute hypomanias has become an important clinical question. Unfortunately, as is common with milder pathological states, no controlled study—with lithium or any other mood stabilizers—has systematically examined the efficacy of a treatment for hypomania. Clinical recommendations typically follow those for treating mania. However, given the inherent lower capacity for functional impairment in hypomania compared to mania, a different treatment algorithm might be in order. Additionally, it makes good clinical sense to distinguish the treatment of hypomania in a bipolar I patient vs. a bipolar II patient. In the former, it is difficult to know if the hypomania is a transitional state in evolution to a full-blown mania or will stay at the milder symptomatic level. In bipolar II patients, in contrast, the likelihood of switching into a full-blown mania is rather low, even with antidepressants. Additionally, there is an increasing recognition that not all hypomanias—especially those in bipolar II patients—need to be treated pharmacologically at all. These recommendations suggest that "watchful watching" may suffice for mild hypomanic episodes in patients who retain insight into their mood states and with whom a therapeutic relationship with their psychiatrist can be well maintained (Parker 2012). Of course, the possibility or even likelihood of a post-hypomanic depression must always be considered as part of an overall treatment strategy with a goal of preventing such episodes.

No study has examined the specific role of lithium in treating acute hypomania. Some small or open studies have examined the efficacy of other agents—risperidone, valproate, quetiapine—in hypomanias (Vieta et al. 2001; McElroy et al. 2010a, b). Theoretically, lithium has a number of advantages in treating acute hypomania: (1) It is not overtly sedating. Since, by definition, hypomania is treated in an outpatient setting, side effect sensitivities are critical. With its inherent lack of sedation, hypomanic patients may find lithium more tolerable than other mood stabilizers such as valproate or some of the antipsychotics that are more likely to be overtly sedating. (2) In treating hypomania, lithium's later and more gradual onset of efficacy compared to antipsychotics may be an advantage. In treating hypomania, there is inherently far less urgency in decreasing symptoms, and the normalization of mood that characterizes lithium's efficacy may make it more acceptable to patients. (3) Since lithium is an excellent overall mood stabilizer with the ability to prevent both depressions and manias (see Chap. 5 for more details), it may help in the prevention of post-hypomanic depressions.

Given the lack of studies in the area, it is impossible to know whether optimal serum lithium levels differ in the treatment of mania vs. hypomania. Because hypomanic patients are not in hospital, it may be prudent to target slightly lower lithium doses/serum levels, in the range of 0.6–0.8 mEq/L initially in contrast to the usual

target levels of 0.8–1.2 mEq/L used in treating acute mania. If the hypomanic patient does not respond sufficiently to the lower level, the dose may then be raised to the usual lithium doses/levels used to treat full-blown manias.

6.7 Lithium's Place in Modern Practice and Treatment Guidelines in the Treatment of Acute Mania

Utilizing published practice and treatment guidelines to create a uniform set of treatment principles in the field is somewhat problematic since these documents differ slightly from each other as a consequence of the different individuals who participated and the local, cultural factors that affect their recommendations. Nonetheless, surveying modern practice guidelines provides some semblance of clinical consensus in the field.

Not surprisingly, all recent treatment guidelines consider lithium as a first-line treatment for the treatment of acute mania (Nivoli et al. 2012). Consistent with the data already reviewed, across different guidelines, it is recommended more for euphoric mania vs. mixed or dysphoric mania. For those with marked psychomotor agitation or behavioral disturbance (presumably very manic hospitalized patients), lithium is recommended more as a second-line treatment unless there is a clear past history of a robust response to lithium in similar circumstances. Similarly, lithium is also recommended for milder vs. more severe manic episodes. For patients already taking lithium who have a breakthrough episode, a serum lithium level should be checked, and the dose should be raised to achieve the full antimanic level (presumably 0.8–1.2 mEq/L). With all acute antimanic agents, including lithium, if no response is seen within 2 weeks, switching to another agent or adding a second antimanic medication would be appropriate. Currently, there are no data suggesting one of these approaches over the other.

In these guidelines, for patients who have not responded to a full monotherapy trial, lithium is recommended as a second-line treatment in combination with another antimanic agent. The other antimanic agent could be valproate, carbamazepine, or an SGA. In clinical practice, however, combination treatment is far more common than is discussed in the various treatment guidelines. As an example, in one study, less than one third of acutely manic hospitalized patients across three European countries were treated with monotherapy with the average patients receiving 3.3 medications (Wolfsperger et al. 2007). By 2004, with the gradual trend toward the use of medications other than lithium to treat acute mania, only 5 % of patients were treated with lithium monotherapy.

Assuredly, the liberal use of polypharmacy reflects a number of factors such as (1) the pressure that clinicians feel to get patients better as quickly as possible, especially when they are hospitalized. This translates to a more aggressive approach—including earlier and more frequent use of combination therapies—that is recommended in these guidelines; (2) subjects in studies are typically less complex with fewer comorbidities than patients seen in ordinary clinical practice. More complex patients are commonly treated with more complex regimens. The price of these

aggressive approaches is the increased side effect burden associated with combination therapy, especially sedation and weight gain. Whether a patient on combination therapy—as example, lithium plus an antipsychotic—needs to be continued on both treatments during continuation and longer-term maintenance treatment is not clear.

For now, then, lithium continues to be a mainstay of treatment for acute mania. Our recommendation is that it can be used as monotherapy—with as needed doses of a tranquilizing agent such as an antipsychotic or a benzodiazepine—for outpatients with mania or inpatients whose manic episode is not characterized by severe frenzied agitation. However, because of the many studies and long clinical experience showing the greater efficacy of combination treatment—especially lithium plus an antipsychotic compared to lithium monotherapy—we recommend the combination treatment for more severe or agitated mania.

6.8 Technical Aspects of Lithium Treatment During Acute Mania

As described in more detail in Chap. 11, a simple set of blood tests should be obtained prior to initiating lithium as a treatment for acute mania. At minimum, this would include a serum creatinine to establish baseline renal function and a thyroid-stimulating hormone (TSH) to establish baseline thyroid function. In occasional cases in which treatment is urgent, there is no reason to suspect thyroid and/or renal dysfunction, and the patient is willing to take lithium but not to allow venipuncture, even these tests may be postponed until the patient allows them to be drawn. Other tests that would be appropriate before starting lithium are a pregnancy test and an electrocardiogram for those over 40 years old.

Initial lithium doses for nongeriatric patients in acute mania are usually 600–900 mg daily, administered as lithium carbonate capsules. For geriatric patients, 300–600 mg would be appropriate starting doses with an occasional older patient started with 150 mg daily. Higher initial doses are typically prescribed for patients who have a past history of lithium treatment that was reasonably well tolerated, younger patients, and hospitalized patients. Optimally, most if not all of the lithium should be administered at night, for convenience, to allow maximal serum levels (and therefore side effects) when the patient is sleeping and possibly to decrease lithium's effects on renal function. (See Chap. 12 for more details.) Patients who experience substantial nausea may need to have a divided dose regimen and/or be switched to one of the sustained release lithium preparations.

As described in Chap. 4, steady-state lithium levels are achieved based on the half-life of lithium which averages 18–24 h but ranges from 12 h in some young, healthy patients to >2 days in elderly patients with more compromised renal function. Since steady state is achieved after five half-lives, for the average adult patient, constant dosing for 5 days would be necessary to obtain a reliable, steady-state lithium level. For acutely manic patients, this is an unacceptably long time frame. It is possible to estimate a steady-state level after 2–3 days by measuring the 12 h level and simply increasing the result by 25 %. Thus, a 3-day lithium level of 0.8 mEq/L is probably

equivalent to a steady-state level of 1.0 mEq/L. Using this scheme, lithium doses can be easily adjusted every few days as needed to achieve the optimal serum level. Typical doses for acute mania range between 900 and 2400 mg daily. However, doses are less relevant than serum levels, which can be checked easily in hospital settings.

In the past, the use of a test dose of lithium followed by a 24 h serum lithium level determination to predict a steady-state level was suggested (Cooper and Simpson 1976). This method is rarely if ever utilized today. The variability in lithium excretion on a day-to-day level while acutely manic, dependent on number of hours slept, activity levels, and so forth makes this model difficult to use. Because of these problems, virtually all clinicians utilize the gradual dose escalation with frequent lithium level monitoring approach discussed above.

Optimal lithium levels in treating acute mania typically range from 0.8 to 1.2 mEq/L. Of course, some manic patients will do well at below this range, while a smaller number will require even higher serum levels. Anecdotally, some adolescents will require and tolerate levels of 1.5 mEq/l. Conversely, geriatric patients are notoriously sensitive to high lithium levels. Some older manic patients will respond to serum levels in the 0.4–0.7 mEq/L range and will show lithium toxicity symptoms at levels above this. (See Chap. 12 for more details about lithium toxicity.) Since lithium levels are exquisitely sensitive to hydration status, care must be taken, especially in severely manic hospitalized patients, to monitor fluid intake in order to avoid preventable episodes of lithium toxicity.

Since maintenance lithium levels are generally lower than those needed to treat acute mania, there is the question of when the lithium dose should be lowered to the target maintenance level. No study has examined this question. A reasonable approach would be to lower the dose/level either when the mania remits or within one to a few weeks thereafter. This is especially relevant since both lithium levels and side effects will increase after the resolution of a mania (see below for details).

6.9 Lithium Side Effects During Acute Treatment

At any phase of treatment, lithium side effects are relevant since they are a most important factor in predicting treatment adherence. However, side effects are generally more important during longer-term maintenance treatment since patients are treated outside hospital during that treatment phase and because some side effects are more relevant over longer time frames. Discontinuation due to adverse events of lithium in acute mania studies ranges between 5 and 15 %. For acute mania, common side effects, discussed in greater detail in Chap. 12, include nausea, tremor, diarrhea, dry mouth, and somnolence and/or fatigue. Vomiting should alert the clinician to the possibility of toxicity and should provoke a lithium serum level determination. Lithium-associated weight gain is not a major issue in acute mania. Side effects are generally dose and serum level related. Many side effects can be handled by simple dose reductions.

Another important issue in managing lithium's side effects during treatment for acute mania is to anticipate the increase in serum level that often occurs upon

resolution of the mania (even assuming complete treatment adherence and no change in sodium intake or hydration). Presumably, this relates to differences in renal blood flow and lithium excretion. Whatever the explanation, clinicians need to monitor bipolar patients carefully during this time and be prepared to decrease the lithium dose in order to avoid lithium toxicity. Additionally, lithium side effects decrease when patients are manic and increase when they are depressed, independent of lithium levels (Wilting et al. 2009). Therefore, following the resolution of a manic episode, patients will have an increase in their lithium level—which will increase side effects—*and* show a heightened sensitivity to these same side effects. These two factors will therefore threaten treatment adherence unless these issues are addressed clinically by lowering the lithium dose to maintenance treatment levels and more aggressively treating side effects if needed. (See Chap. 12 for treatment of troublesome lithium side effects.)

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Treatment of Depression with Lithium

7

7.1 Introduction

In contrast to the consistent positive results seen with lithium in treating acute mania, regardless of the varied methodologies used, the efficacy of lithium for acute depression has been controversial from the earliest clinical observations. In Cade's early work, lithium did not appear to be effective in treating chronic depression. A decade later, Schou also found little efficacy for lithium in treating endogenous depression (Johnson 1984). Even in 1968, Schou concluded that lithium is of little to no value in severe depression (Schou 1968). However, over the subsequent decade, a handful of studies revisited this issue with somewhat more encouraging results. As with the early studies in acute mania, methodological issues made the results of these early studies difficult to interpret. These included the mixture of unipolar and bipolar depressed patients, the small number of subjects, and the use of active comparators but *not* placebos in many studies. The results of some studies suggested that lithium might be more effective in bipolar depression than unipolar depression but this too was unclear.

Now, many decades later, the place of lithium in treating acute depression continues to be uncertain. Recent studies examining its role in depression, especially in comparison to other modern agents, are few. However, beyond its efficacy as a monotherapy in depression, lithium has also been evaluated as an adjunctive treatment for unipolar depression, added to an antidepressant. A few studies have additionally evaluated lithium's role as an antidepressant-accelerating strategy. Another potential role for lithium—in the treatment/prevention of suicidality—is discussed in Chap. 8. Lithium's efficacy in preventing depressive episodes is covered in Chap. 5.

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7.2 Lithium's Efficacy as Monotherapy in Unipolar and Bipolar Depression

A number of early studies evaluated lithium's efficacy for acute depression. As with the database examining other uses of lithium from that era, non-modern research methods, including the frequent use of crossover designs, make the interpretation of these studies difficult. Nonetheless, a meta-analysis of these early studies indicated efficacy in the treatment of acute bipolar depression from the results of a few small studies (Souza and Goodwin 1991). For unipolar depression, the efficacy of lithium compared to placebo is less clear. Comparing lithium to antidepressants in these early studies, efficacy seemed comparable. However, since these studies did not employ a placebo control, conclusions must be tentative. Acknowledging the research design problems, a more recent analysis of these early studies found both overall efficacy of lithium over placebo for acute depression (relative risk = 4.85, $p = .0007$) and greater efficacy in bipolar vs. unipolar depression (relative risk = 2.4, $p = .005$) (Selle et al. 2014).

Among recent studies, using modern methodology, only one controlled study has examined lithium's efficacy in acute bipolar depression (Young et al. 2010). The goal of this study was to evaluate the efficacy of quetiapine but used lithium with target lithium levels of 0.6–1.2 mEq/L as an active comparator along with placebo in a double-blind, random assignment study of bipolar I and II depression. Unfortunately, placebo response and remission rates in this study were rather high, 56 % and 55 %, respectively. Lithium response and remission rates were 63 %, a nonsignificant difference from placebo. Separating the data between bipolar I and bipolar II patients did not demonstrate differential lithium efficacy. However, in this study, the high placebo response and, especially, remission rate reduce the possibility of finding a significant difference from placebo (although quetiapine was found to be significantly more effective than placebo). The relatively low mean lithium level in this study—the majority did not achieve levels above 0.6 mEq/L—may have also contributed to the lack of separation between lithium and placebo. (However, the subgroup of patients with levels above 0.8 mEq/L showed similar results with lithium not more effective than placebo.)

Three other recent studies evaluated lithium's efficacy in acute depression, two in bipolar depression (Suppes et al. 2008; Machado-Vieira et al. 2014) and one in unipolar patients (Bschor et al. 2013). In the first bipolar depression study, patients with bipolar II depression were randomly but openly assigned to lamotrigine or lithium for 16 weeks. Comparable efficacy was seen in the two groups (Suppes et al. 2008). Lithium was associated with more side effects, but no difference was seen in dropout rates. In the second bipolar study (Machado-Vieira et al. 2014), both bipolar I and bipolar II depressed patients were treated openly with lithium. The remission rate after 6 weeks was 62 %.

In the one recent unipolar depression study, lithium was compared with the selective serotonin reuptake inhibitor (SSRI), citalopram, in an open assignment 4-week study (Bschor et al. 2013). This is the only study comparing lithium to a modern antidepressant. Of note, it did not employ a random assignment or

double-blind design (Surprisingly, there are no studies with the classic modern design evaluating lithium's comparative efficacy to a modern antidepressant in unipolar depression). Lithium was generally less effective than citalopram. However, the subgroup of patients with recurrent depressive episodes responded much better to lithium than did those presenting with a first, nonrecurrent course (68 % vs. 0 %), a predictor not found in the citalopram group. The implication is that lithium's efficacy may be maximal in recurrent mood disorders, regardless of polarity.

7.3 Lithium as an Adjunctive Antidepressant

Far more common than lithium's use as a monotherapy for either unipolar or bipolar depression is its addition to an ongoing antidepressant that did not adequately treat unipolar depression. The first report of lithium's efficacy in this area was published in 1981 (DeMontigny et al. 1981). Using an open design, lithium was associated with improvement in depressive symptoms within 48 h in a small group of patients. The speed with which lithium seemed to work in this study has not been replicated in the many trials of adjunctive lithium published since then.

Ten placebo-controlled trials suitable for meta-analysis have been published in this area (Crossley and Bauer 2007; Nelson et al. 2014; Bauer et al. 2014). The vast majority of the subjects in these trials (total $n=269$) were unipolar depressed patients, with most treated for major depression. A small number of subjects were dysthymic ($n=7$), while an equally small number ($n=10$) were bipolar depressed patients. The number of bipolar subjects in these studies is too small to be analyzed separately. Usual lithium doses were 600–900 mg daily. No evidence exists that higher doses than this range confer greater efficacy. Overall, lithium was more effective than placebo when prescribed as an adjunctive agent with odds ratio of 3.11 and 2.89 in the two meta-analyses. The number to treat (NNT) for adjunctive lithium is 5, indicating a substantial clinical effect. (The NNT for lithium as an antimanic agent is also 5.)

Of the adjunctive lithium studies, only three studies utilized modern antidepressants, with less than 100 total subjects evaluated. In this subgroup of patients too, lithium was also significantly more effective than placebo. The relative efficacy of lithium with modern antidepressants was not different from that seen with tricyclic and other older antidepressants (Nelson et al. 2014).

A relatively small number of studies have compared lithium's antidepressant adjunctive efficacy to other treatment strategies, such as increasing antidepressant doses, adding a second antidepressant, adjunctive antipsychotics, or adjunctive T3 (triiodothyronine). The usual methodological problems such as non-double-blind design and/or a small number of subjects evaluated plague a number of these studies. In general, lithium was found to be equivalently effective to the other strategies. In one small n study, lithium and T3 were equally effective as adjunctive treatments, and both were significantly more effective than placebo (Joffe et al. 1993). In the large STAR*D study, which used a random assignment but nonblinded design, lithium and T3 were equally and relatively ineffective with remission rates of 16 % and

25 %, respectively (Nierenberg et al. 2006). Because this was the third step in a multistep algorithm study, these subjects in this study were more treatment resistant than in many other studies. Additionally, since there was no serum lithium level monitoring nor systematic dose adjustment, the STAR*D study cannot be meaningfully compared to the placebo-controlled trials of lithium. Compared to T3, lithium was less well tolerated. In the largest recent nonblinded random assignment study, adjunctive lithium was equally effective to adjunctive quetiapine in depressed patients who failed to respond to a full antidepressant trial (Bauer et al. 2013a).

Another question regarding the use of lithium as an adjunctive agent is the proper length of time a patient who has responded should remain on lithium (presumably along with the antidepressant). In the only good study in this area, patients with unipolar depression who responded to adjunctive lithium during a 6 week open trial and who continued lithium had significantly fewer relapses compared to those switched to placebo (0 % relapse vs. 46 %, respectively) in a double-blind fashion (Bauer et al. 2000). Because even more patients relapsed after open withdrawal of lithium, the reasonable recommendation was and is to continue adjunctive lithium for at least 1 year (Bschor et al. 2002).

Despite the strength of the database supporting lithium's efficacy as an adjunctive treatment, it is used surprisingly infrequently, at least in the United States. In a large pharmacy database study in the US Veterans' Administration system, only 0.5 % of depressed patients treated with a second (and therefore adjunctive) agent were prescribed with lithium (Valenstein et al. 2006). Far more patients were prescribed second-generation antipsychotics or a second antidepressant. It is not obvious why lithium is so underutilized in the United States as an adjunctive agent. Side effect burden should always be considered as a factor. Yet, a number of the adjunctive studies—which were short term, up to 6 weeks—did not find significantly higher discontinuation rates from lithium compared to other agents. In contrast, the STAR*D study did find a greater discontinuation rate with lithium vs. T3 (Nierenberg et al. 2006). Blood level monitoring not required with any other psychopharmacological approaches for depression might also explain lithium's underutilization. No study has investigated this possibility. Finally, the concerns about long-term effects, such as renal effects, discussed in Chap. 12, may also dissuade psychiatrists and patients alike from prescribing adjunctive lithium. In contrast to the United States, European psychiatrists prescribe adjunctive lithium more frequently, and it is recommended as a first-line adjunctive treatment by practice guidelines such as those from Germany.

7.4 Combination Treatments with Lithium

Another possible method of using lithium for acute depression is by combining it with other treatments. In some studies (and in some clinical situations), the paradigm is of adding another agent to lithium that has not been effective. Two recent studies have utilized this design. In one study, bipolar depressed patients already treated with maintenance lithium at levels between 0.6 and 1.2 mEq/L who were

still symptomatic were given lamotrigine, titrated to 200 mg daily vs. placebo (van der Loos et al. 2009). The combination was significantly more effective than lithium alone. Further addition of paroxetine in lamotrigine nonresponders was not helpful, but paroxetine was helpful when added to lithium alone (Van der Loos et al. 2010). In the other study, in a small double-blind not placebo-controlled study, paroxetine and amitriptyline were equally effective when added to lithium (Pilhatsch et al. 2010). Of course, both of these studies tested the efficacy of the second agent rather than evaluating the efficacy of lithium.

In other clinical situations and studies, lithium is part of a combination strategy that is employed de novo. In one of these studies, lithium efficacy for bipolar depression was compared to lithium plus an antidepressant, either paroxetine or imipramine (Nemeroff et al. 2001). In contrast to the results seen with all subjects, those with higher lithium levels—0.8 mEq/L or above—did not demonstrate an enhanced response to the antidepressant, implying that higher lithium levels should be prescribed prior to adding a second agent such as an antidepressant.

More recently, the efficacy of lithium in combination with total sleep deprivation and morning bright light therapy was evaluated in hospitalized bipolar I depressed patients. In a large but open study, the response to this combination was 50 % within 1 week with a dramatic decrease in suicidality (Benedetti et al. 2014). For more than half the acute responders, the response maintained for at least 1 month. Because this was a study of hospitalized patients, it is unclear whether this strategy would work as well with outpatient bipolar depressed individuals. Total sleep deprivation is problematic in outpatient depressed patients since staying up all night typically requires other individuals—such as nurses—to promote all night wakefulness. Since this study was open with neither blinding nor any control condition, whether this multimodal treatment would work as well when compared to some other treatment is also unclear.

None of these combination approaches with lithium establish specific antidepressant for lithium as monotherapy Nonetheless, these studies point to the possibility of creative approaches in combination treatments with lithium in treating depression.

7.5 Lithium as an Antidepressant Accelerator

The goal of an acceleration strategy is to speed up an antidepressant response, regardless of whether, at the end of a 6–8-week trial, the accelerator is associated with higher response and remission rates. To test an accelerator, one compares the time to onset of efficacy of the antidepressant plus placebo to an antidepressant plus an accelerator which is started at the initiation of treatment. Despite the universal frustration about the delayed onset of antidepressant efficacy, acceleration strategies have, in general, not been pursued nearly as much as augmentation strategies.

Lithium has been evaluated as an accelerator in five placebo-controlled studies with a total of only 231 subjects (Crossley and Bauer 2007). Studies included both unipolar and bipolar patients, and antidepressants used in the studies were all

tricyclics or maprotiline. No acceleration studies with modern antidepressants are available. Overall, in a meta-analysis measuring changes in depression scores, lithium accelerated the antidepressant effect at a trend level ($p = .09$), indicating a weak effect (Crossley and Bauer 2007). Examining response rates also showed a positive but not significant effect of lithium as an accelerator. The absence of any lithium acceleration studies using modern antidepressants and the lack of distinct databases for unipolar vs. bipolar depression remain a major deficit in this area. For now then, lithium's efficacy as an antidepressant accelerator remains uncertain.

7.6 Predictors of Response to Lithium as an Antidepressant

Unfortunately, no validated predictors for lithium's antidepressant effect exist. As noted above, some evidence suggests that bipolar depressed patients may show a better response compared to unipolar depressed individuals. Some, but not all studies suggest that more severely depressed patients may respond better. Among unipolar patients, clinical factors suggestive of a bipolar spectrum disorder, such as family history of bipolar disorder, cyclothymic personality features, early illness onset, and postpartum depression, may predict a better response to lithium as monotherapy (Bauer et al. 2006).

For lithium's adjunctive efficacy in unipolar depressed patients, there are also no validated predictors. A meta-analysis suggested that shorter studies found a greater lithium vs. placebo difference, suggesting the possibility of a later effect from the primary antidepressant (Nelson et al. 2014). Neither age nor gender predicts an adjunctive lithium response. The relationship between depression severity and adjunctive lithium response is unclear with some, but not all studies finding that more depressed patients do better with lithium. Unfortunately, whether the level of treatment resistance, typically calculated as the number of failed antidepressant trials, predicts adjunctive lithium response is unclear because too few studies evaluated this variable.

7.7 Lithium's Antidepressant Role in Treatment/Practice Guidelines

Consistent with the data reviewed above, lithium's role in treating acute bipolar depression hovers between first- and second-line treatments, depending on the specific guidelines (Nivoli et al. 2011). It is frequently recommended in combination with other treatments such as lamotrigine (in part because of the van der Loos study [2009] described above), divalproex, antidepressants, or as an adjunctive treatment. In those guidelines that distinguish between bipolar I and bipolar II depression, lithium's place is somewhat lower for the latter, based on both a relative lack of evidence due to inadequate study and the greater treatment flexibility in treatment options for bipolar II depressed patients, given their lower risk of switching with antidepressants.

Treatment guidelines (e.g., the World Federation of Societies of Biological Psychiatry) for unipolar depression generally support adjunctive lithium as a first-line treatment for patients failing to respond to an antidepressant despite the relative paucity of data when it is prescribed in combination with modern antidepressants (Bauer et al. 2013b).

7.8 Techniques of Administration for Lithium's Use as an Antidepressant

Both the target doses and blood levels are lower, and the speed of dose titration is slower when lithium is prescribed for depression vs. mania. This reflects a number of factors including (1) the lesser urgency in treating depression since most depressed patients are treated as outpatients vs. the usual inpatient setting for acute mania; (2) the heightened sensitivity to side effects in depressed vs. manic patients, thereby requiring a slower dose titration; and (3) the probable need for lower lithium plasma levels in depression vs. mania.

For acute unipolar depression and for augmentation depression treatment, target serum levels are usually recommended as 0.6–0.8 mEq/L. An earlier study found that very low dose lithium (250 mg) was less effective than 750 mg when prescribed as an augmentation treatment to a tricyclic antidepressant (Stein and Bernadt 1993). For augmentation, once the target serum level is achieved, 2 weeks at that dose constitutes a reasonable trial. If no effect is seen after 2 weeks, adjunctive lithium should be discontinued and another approach utilized. A reasonable dose titration would be to start at 450 mg, increasing to 900 mg on day 2. Doses should then be adjusted to achieve the target serum level of 0.6–0.8 mEq/l. Divided doses vs. once-daily doses at night should be decided on the basis of nausea. In the absence of nausea, nighttime dosing is preferred; if nausea is problematic, divided dose administration after eating should be considered.

Pre-lithium laboratory tests are the same with depression as they are for other uses (see Chaps. 6 and 11 for details). Since a lithium antidepressant trial is relatively brief, measured in weeks, not months, no monitoring of renal or thyroid function is needed during the acute antidepressant trial. If the patient responds and lithium is continued as a longer-term maintenance treatment, monitoring should be done as described in Chap. 11.

Side effects seen with lithium when prescribed for depression are the same as those seen in acute mania and maintenance treatment (see Chaps. 6 and 12 for details). It is important to remember that depressed patients relative to manic patients are more sensitive to side effects. Therefore, clinicians need to be especially attentive to these issues in order to maximize treatment adherence.

7.9 Place of Lithium in the Treatment of Acute Depression

Given the information just reviewed, what is lithium's place in the treatment of depression? Table 7.1 summarizes our view.

Table 7.1 Lithium's place in treating unipolar depression

Clinical situation	Data	Comment
Bipolar depression	++	Early data positive. One negative recent study
Unipolar depression	+	Weak data
Adjunctive treatment in unipolar depression	+++	Data solid: underutilized
Accelerator agent for depression	+	More study needed

For the treatment of acute depression, distinguishing between unipolar and bipolar depression is highly relevant. For bipolar depression, lithium should be considered a viable initial treatment strategy. Although the data supporting its use as a first-line agent for bipolar depression remains relatively weak, with the one modern study finding no difference in efficacy between lithium and placebo (Young et al. 2010), the older studies suggest better efficacy. Additionally, since bipolar patients will inevitably need to be on a mood stabilizer for longer-term mood episode prevention, initiating a long-term treatment during an acute episode that can then be continued has great appeal. Lithium's relatively slow time to efficacy for acute depression makes lithium a better strategy when the depression is mild to moderate. Although lithium is certainly not the only first-line option for acute bipolar depression, it should properly be considered first line.

For unipolar depressed patients, although lithium remains an option, it should not be considered as highly as others such as antidepressants. The data in support of its use with acute unipolar depression is much weaker compared to bipolar depression, and many other options are better validated. Additionally, since the risks of antidepressant-driven pharmacological mania/hypomania are relatively small in treating unipolar depression and the place of maintenance treatment in these patients is not as universal, the advantages of lithium are diminished. In contrast to its use as monotherapy, lithium continues to be a strong first-line adjunctive treatment in unipolar depression. As noted, the disparity between the data supporting its use and the infrequency with which it is prescribed—especially in the United States—remains somewhat of a mystery.

Additionally, other options for those who fail to respond to an antidepressant—switching to a different agent, adding another antidepressant, adjunctive thyroid hormone, adjunctive second-generation antipsychotic, and so forth—provide patients and clinicians with choices that are relatively simple, and many of which (but not all) are more easily tolerated than lithium. Of note, however, many of these other agents have far less evidence for their efficacy as adjunctive antidepressants than does lithium. Overall, lithium should be more highly considered as an adjunctive agent than the naturalistic data on its use suggest.

The acceleration data for lithium are rather weak and it is infrequently prescribed for this purpose. It must be acknowledged, however, that no other accelerator agents—T3, pindolol—are used with any regularity by clinicians. Here too, it is unclear why this is such an infrequently used strategy given the universal frustration with the slow speed of onset of antidepressant efficacy. For now then, lithium is one

of many possibly effective accelerator agents that is unlikely to be prescribed with any frequency. Having even one study that examines lithium as an accelerator to a modern antidepressant would certainly help refocus the field in this direction.

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Suicide Prevention with Lithium

8

8.1 Introduction

Suicide is the most tragic outcome and deepest worry for all people suffering from mood disorders and for those treating these individuals. The risk of completed suicide is considerable and about 20 times higher in patients with mood disorders than in the general population (Harris and Barraclough 1997). Among the mental disorders, depression is associated with the highest suicide risk, with more than 50 % of all people who die by suicide suffering from a current depressive disorder. Suicidal ideation and behavior (suicidality) is an even more common phenomenon. As an example, in an observational study called EMBLEM of 2,219 patients with bipolar disorder, 663 people (29.9 %) reported at least one suicide attempt based on lifetime history (Bellivier et al. 2011). The exact percentage of people with mood disorders who commit suicide over lifetime is unknown, but estimates are around 10–20 %.

Suicide is a global phenomenon. In a recent report, the WHO (the World Health Organization) found that more than 800,000 people die by suicide every year, almost one person every 40 seconds. Although suicide occurs all over the world, approximately 75 % of all suicides occur in low- and middle-income countries. It is observed in all age groups, but the highest rates are found in people aged 70 and older. However, suicide is also the second leading cause of death in 15–29 year olds (partly because of the lower prevalence of other causes of death in young people). In most countries, suicide is more prevalent among men.

Suicide rates of people with bipolar and unipolar depressive disorders have been found to be equal, although a longitudinal study from Switzerland reported higher rates of suicide completion in unipolar depressed than in bipolar patients, especially those in whom mania predominates (Angst et al. 2005). Not surprisingly, suicide is most likely during the depressed phase of the disorder. Furthermore, the risk of suicide is high during the course of rapid cycling and mixed episodes. Completed suicides and suicide attempts are relatively more common in younger bipolar disorder sufferers, but it can occur at any age.

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8.2 Evaluation of Suicidality

Suicidality must be approached openly with the patient and, whenever possible, with family members. Unfortunately, there is no perfect assessment tool that predicts who will make a suicide attempt. In bipolar disorder, most suicides happen during the phases of depression or a mixed episode. Features such as a history of past attempts, family history of suicide, and recent stressful life events, especially loss, feelings of hopelessness, and substance abuse, are known to increase an individual's risk and should be evaluated during the clinical assessment. Of these, the most important and the most predictive is a history of past suicide attempts. Therefore, probing carefully and specifically addressing this one simple part of the patient's history are crucial. Close psychiatric evaluation including hospitalization is essential for patients at high risk for suicide (Miklowitz and Gitlin 2014).

8.3 Treatment of Suicidality

Due to the complexity and nature of suicidality, treating suicidal patients is one of the most challenging tasks for healthcare professionals. The high mortality, morbidity, and costs related to attempted suicide, the development of treatment, and the prevention strategies for suicidal behavior have been the focus for much of the research on suicidality. Constructing suicide prevention strategies is of great importance and should include all facets of influence on suicidal behavior including pharmacological, psychological/psychotherapeutic, and sociological methods. Not only is there a need for more research on the neurobiological underpinnings in the evolution of psychiatric diseases (as one of the most important risk factors for suicide) and suicidality, more research on effective therapeutic strategies is also urgently needed (Müller-Oerlinghausen and Lewitzka 2016).

Unfortunately, available options for the clinical management of suicidal patients are mostly empirical and lack rigorous scientific proof. These include psychological, pharmacological, and other biological treatment options. There is no doubt that, although psychological support for suicidal patients is essential, the evidence-based support for an effective reduction in suicidal risk by psychotherapeutic interventions is limited (Tondo and Baldessarini 2015). Physicians typically administer antidepressants, benzodiazepines, and antipsychotics to treat suicidality, but there is no proof that any of these medications demonstrate acute "anti-suicide" efficacy. This is most relevant for antidepressants because their use may even increase suicidality, at least temporarily early in treatment in young people aged below 25, who become more agitated, irritable, and restless shortly after initiation of treatment with antidepressants (Gunnell et al. 2005). This phenomenon led the FDA to issue regulatory warnings on these drugs (Fergusson et al. 2005).

For only two medications, namely, lithium and clozapine, there is at least some solid research evidence that suicide may be prevented in long-term treatment. For clozapine, an atypical antipsychotic, such effects have only been explored in research studies in schizophrenia (Meltzer et al. 2003; Müller-Oerlinghausen and Lewitzka 2016).

8.4 Lithium Protection Against Suicide

Lithium has been by far the medication evaluated in the greatest number of trials for its anti-suicide effects. Since the early 1970s, several reports and studies from various research groups in different countries confirmed the finding that long-term lithium therapy may lower suicide rates (reviewed in Lewitzka et al. 2015b). Despite convergent evidence and corresponding recommendations in national and international guidelines on the lithium's use for the acute and maintenance therapy of mood disorders (WFSBP Grunze et al. 2013), its use to prevent suicide is still relatively uncommon in clinical practice.

8.4.1 How It All Started

One of the first descriptions of lithium's anti-suicidal properties dates back to 1972 when Barraclough described the current and past clinical history of 100 suicide cases in England (Barraclough 1972). He postulated that as many as a fifth of those suicides may have been prevented had lithium been used. In 1977, the American psychiatrist Fieve reported that no suicidal acts were observed in 20 patients on long-term lithium treatment (78 weeks), demonstrating evidence for the anti-suicidal effects of this drug. Hanus and Zapletálek (1984) in Czechoslovakia came to similar conclusions when they analyzed data from 95 patients who were taking lithium for approximately 5 years and compared suicide attempt rates during that treatment time to a past time without lithium therapy. They observed a 20 % reduction in suicide attempts. In the early 1990s, British researchers analyzed the mortality of 103 patients attending a specialized lithium clinic: only ten patients died during the study of causes unrelated to treatment (Coppen et al. 1991). Interestingly, the expected number of deaths due to suicide in their sample was 18.3, and considering no deaths from suicide were observed, their findings suggest that lithium reversed the excess mortality associated with recurrent mood disorders, including that from suicide. However, another study from Denmark demonstrated no advantage of lithium in terms of the overall mortality in 133 patients with mood disorders followed for 5 years while taking lithium (Vestergaard and Aagaard 1991).

In 1992, in a large international study comprising 827 lithium-treated patients with mood disorders, researchers from the International Group for the Study of Lithium-Treated Patients (IGSLi) demonstrated that their mortality did not differ from a matched healthy population's. Epidemiological studies indicate a two- to threefold higher standardized mortality in untreated bipolar patients than in the general population. Another group also studied the occurrence of suicides and suicide attempts in 68 patients with mood disorders and a history of suicide attempts while on and off lithium treatment. They observed only one suicide in patients with regular lithium intake. Eleven of thirteen patients revealed suicidal or parasuicidal behavior after discontinuing lithium, which the authors suggested to be an indication of lithium's anti-suicidal effect independent of the general episode suppressing effect (Müller-Oerlinghausen et al. 1992). Later, Felber and Kyber (1994) in

Germany detected a 10 to 1 reduction in suicide attempts and a 3 to 1 reduction in the number of suicides in patients taking lithium compared to an untreated period. A Swedish study of 362 patients with mood disorders found that the relative risk of suicide was 4.8 times higher when patients were off lithium than when taking it (Nilsson 1995).

Lithium's anti-suicidal effect has even been documented across different lithium response categories. For example, Ahrens and Müller-Oerlinghausen (2001) observed a reduction in suicide attempts not only in the excellent lithium responders but also among patients exhibiting a moderate to poor response to lithium. This adds further evidence that lithium may possess a suicide-protective effect independent of its mood-stabilizing properties.

8.4.2 Epidemiologically Based Evidence

There is also compelling evidence from epidemiological studies that lithium exerts anti-suicidal effects. In 2003, Goodwin et al. reported on a large US-based sample of 20,623 health-insured patients with bipolar disorder. Patients who had received lithium had a 1.5–3-fold reduced risk of suicide or suicide attempts compared to patients receiving valproate. Kessing et al. (2005) analyzed data from 13,186 patients in a Danish national registry who had received one or more prescriptions for lithium and compared these to the general population who had never been prescribed lithium. Patients who purchased lithium had a higher suicide rate than persons who did not purchase lithium. Purchasing lithium at least twice was associated with a 0.44 lower rate of suicide (95 % confidence interval, 0.28–0.70) compared with the rate when purchasing lithium only once. Furthermore, the rate of suicide dropped with the number of lithium prescriptions (Kessing et al. 2005). Findings from the longitudinal Zurich cohort study, which followed 406 patients with mood disorders for over 40 years (Angst et al. 2005), reported a lower mortality rate among patients treated with lithium. The mortality rate among the lithium-treated patients did not differ from that in the general population. Collins and McFarland (2008) investigated 12,662 Medicaid patients in the United States, demonstrating that lithium-treated bipolar patients had the lowest number of suicide attempts compared to patients taking other mood stabilizers.

8.4.3 Controlled Studies and Systematic Reviews

One placebo-controlled randomized multicenter trial was designed specifically to investigate the influence of lithium on suicidal behavior in bipolar and unipolar depressed patients during a 1 year period (Lauterbach et al. 2008). All participants received standard care, one group received lithium additionally, the other placebo. The analysis of the primary outcome measure indicated no significant difference in suicidal acts between lithium and placebo-treated individuals (adjusted hazard ratio 0.517; 95 % CI 0.18–1.43). However, a post hoc analysis revealed that all completed suicides had occurred in the placebo group, accounting for a significant difference in incidence rates ($P=0.049$):

within a 1 year treatment period, no suicides occurred within the lithium group ($n=84$), whereas three suicides occurred within the placebo group ($n=83$).

Several systematic reviews and meta-analyses have concluded that the rates of suicide and suicide attempts were strikingly reduced when patients diagnosed with bipolar disorder, major depressive disorder, and schizoaffective disorder were receiving maintenance lithium treatment (Cipriani et al. 2005; Baldessarini et al. 2006; Guzzetta et al. 2007). Even bipolar patients who experienced a poor response to lithium have shown a reduction in suicide attempts, suggesting that the anti-suicidal effects of lithium treatment may be independent of its antidepressant and/or mood-stabilizing effects, possibly conferred by a reduction in impulsivity and aggression (Ahrens and Müller-Oerlinghausen 2001; Müller-Oerlinghausen and Lewitzka 2010).

One of the first reviews examining suicide and suicide attempts in patients with mood disorders was in 1997 (Tondo et al. 1997). The authors demonstrated in a pooled sample of more than 17,000 individuals that the suicide risk decreased by 8.6 times in patients treated with lithium compared to patients not taking lithium. Another meta-analysis included more than 3,000 patients and confirmed a lower level of suicide or suicidal events and reduced overall mortality among lithium-treated patients with mood disorders compared to patients taking other medications (Cipriani et al. 2005). The same group of researchers recently published an updated systematic review and meta-analysis of randomized controlled trials showing lithium's efficacy in reducing the suicide risk in patients with mood disorders (Cipriani et al. 2013).

When analyzing data from 328 Sardinian patients with unipolar depression, Italian researchers detected a significantly lower risk for suicide attempts and suicides in lithium-treated patients (Guzzetta et al. 2007).

8.5 Lithium's Suicide-Preventing Effects: Clinical Implications

Long-term treatment with lithium is recommended when the risk of suicide is high. An algorithm when lithium therapy should be considered as a suicide-preventing medication in patients with bipolar disorder is shown in Fig. 8.1 (Lewitzka and Bauer 2014).

Several questions arise when lithium is being considered for suicide prevention. First, the optimal serum lithium level to obtain anti-suicide effects in patients with mood disorders is still unknown. The long-term studies demonstrating suicide-preventing effects administered lithium serum levels within the range of what is considered most effective to prevent future mood episodes (0.6–1.0 mEq/l). Considering that low to moderate doses of lithium leading to blood levels in the 0.3–0.5 mEq/l range have not been effective in treating patients with bipolar disorder (Nolen and Weisler 2013), the standard blood levels (0.6–1.0 mEq/l) are recommended.

On the other hand, a puzzling fact is revealed in several studies that showed that the concentration of lithium in drinking water—which is markedly lower than the therapeutic dose in lithium medication—might correlate with a lower suicide rate. Second, the minimum duration of lithium treatment required to achieve a decrease in suicidality is also unknown. Both these puzzling facts are discussed below.

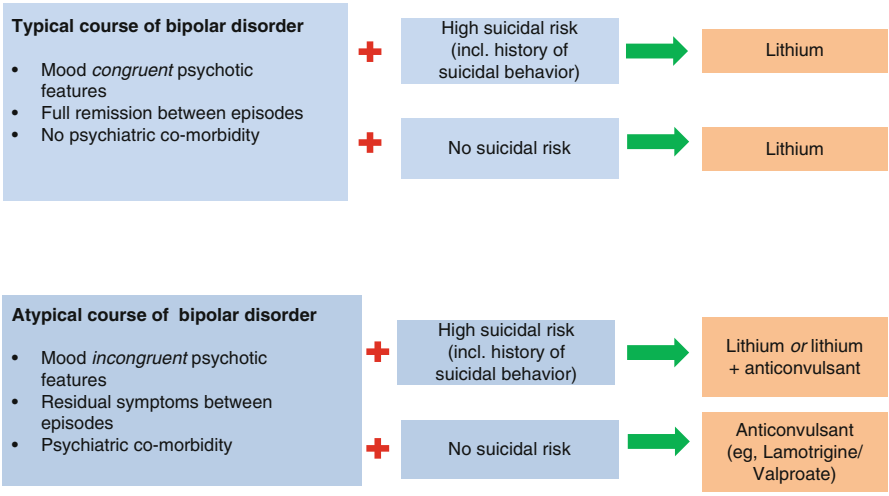

Fig. 8.1 Algorithm when lithium therapy should be considered as suicide-preventing medication in patients with bipolar disorder

8.6 Suicide-Preventing Effects of Lithium as a Trace Element in Drinking Water

A different approach in examining lithium's suicide-protective effects is to determine the ecological association between suicide rates and lithium in drinking water. Lithium is a naturally occurring element, not a molecule like most medications. For example, it is present in the United States, depending on the geographic area, at concentrations that can range widely, from undetectable to around 170 mg per liter. Although it seems odd that microscopic amounts of lithium found in groundwater and food could have any substantial medical impact, researchers began to wonder whether low levels of lithium might correlate with poor behavioral outcomes in humans. Evidence from several controlled studies in various countries (Japan, Austria, the United States) suggests that relatively low doses of lithium can have beneficial effects on suicide rates in the population. A recent comprehensive review supports this association (Vita et al. 2015).

8.7 Does Lithium Also Reduce *Acute* Suicidal Ideation and Behavior?

As outlined earlier in this chapter, lithium seems to exert suicide-preventing effects in the long-term treatment of patients with mood disorders. The next logical question is: Does treatment with lithium also reduce *acute* suicidal ideation and behavior? Clinical evidence from case reports indicate that this effect may occur early on at the beginning of lithium treatment—within days and a few weeks. However,

beyond such anecdotal experiences, the impact of lithium treatment on acute suicidal thoughts and/or behavior has not been systematically studied in a controlled trial. An ongoing research study is testing the hypothesis that lithium plus treatment as usual (TAU), compared to placebo plus TAU, results in a significantly greater decrease in suicidal ideation and/or behavior over 5 weeks in inpatients with a major depressive episode (Lewitzka et al. 2015a). These study results will hopefully provide novel information that could lead to better pharmacological treatment for patients experiencing an acute depressive episode with suicidality and may help reduce the immense individual distress for families in which a member is suffering from depression with acute suicidality.

8.8 Potential Mechanisms of Action in Lithium's Anti-suicide Effects

The neurobiological mechanisms underlying lithium's anti-suicide effect are unknown, but some hypotheses have been made. Lithium differs from other mood stabilizers and from most antidepressants by its marked serotonin agonistic effects related predominantly to its presynaptic functions (Müller-Oerlinghausen 1985). It has been hypothesized that lithium's serotonergic action, possibly in connection with other effects, is related to its well-established antiaggressive effects in animal studies as well as humans (Nilsson 1993) but also to its anti-suicidal effects (Müller-Oerlinghausen and Lewitzka 2010). In one of the rare animal studies focusing on the potential neurobiological underpinnings of lithium's clinical effects, Ohmura et al. (2012) found that lithium may suppress impulsive behavior and thereby decrease the suicide risk. Shock-induced aggression was also attenuated by lithium, as shown in studies with mice (Kovacsics and Gould 2010). Other neurobiological research has focused on lithium's influence on other neurotransmitters such as noradrenalin and dopamine, cortisol stress hormone system, γ-aminobutyric acid, and second messenger systems such as the inositol metabolism, glycogen synthase kinase-3, and more (see also Chap. 4), but the most convincing hypothesis is that lithium leads to a decrease in impulsivity and aggression via several influences on the serotonin system (Müller-Oerlinghausen and Lewitzka 2016).

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Neuroprotection and Other Clinical Indications of Lithium

9

9.1 Introduction

Lithium's mood-stabilizing, antidepressant, and antimanic therapeutic effects are well established. Besides these "traditional" effects, its neuroprotective properties and efficacy in other psychiatric and nonpsychiatric conditions have been tested in clinical settings. Due to the diversity of lithium's pharmacological effects, it is obvious that lithium might be a promising therapeutic option in numerous disorders, although solid scientific evidence is lacking for most of these potential (novel) indications to date.

The pharmacologic mechanisms mediating the neuroprotective effects of lithium and their clinical implications have undergone recent review (Forlenza et al. 2014; Vo et al. 2015). The evidence for lithium's neuroprotective potential suggests its use in clinical research especially for the treatment of neurodegenerative disorders like mild cognitive impairment and dementia (Forlenza et al. 2014). In this respect, the prevention of neurodegenerative disorders primarily in patients already being treated with lithium for other psychiatric indications has become a worthwhile field of research (Nunes et al. 2007). Despite its being a hope-raising therapeutic option for many not-yet-approved conditions, the off-label use of lithium is limited by its narrow therapeutic index. However, as with its use in mood disorders, it has been shown to be a safe and reasonably well-tolerated drug in the studies conducted so far (Hampel et al. 2009).

9.2 Lithium: Neurobiology of Neuroprotection

Lithium's effects on neuronal homeostasis, which involves activating neurotrophic responses, modulating oxidative stress and inflammatory signals, and enhancing mitochondrial function, are associated with neuroprotective properties (Forlenza et al. 2014). To describe the neurobiological effects presumably accounting for its neuroprotective potential, the diversity of lithium's mode of action needs to be

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illustrated (see Chap. 4). Lithium influences cell-surface receptors, second messenger systems, and other signaling molecules (Pasquali et al. 2010) and competes with magnesium for enzyme-binding sites, potentially leading to the inhibition of various enzymes depending on magnesium as a cofactor. In this context, two major targets of lithium are glycogen synthase kinase-3β (GSK-3β) and inositol monophosphatase (IMPase), two enzymes influencing cytoskeletal metabolism and autophagy—two processes closely connected to the broad field of neuroprotection by enhancing cell survival (Forlenza et al. 2014). Furthermore, lithium promotes neuronal cell survival by increasing the expression of anti-apoptotic and inhibiting the expression of pro-apoptotic proteins (Chen and Chuang 1999). Lithium demonstrates additional neuroprotective effects by stimulating the expression and release of neurotrophic factors like BDNF (brain-derived neurotrophic factor) and VEGF (vascular endothelial growth factor) (Forlenza et al. 2014).

Another mechanism by which lithium's neuroprotective potential is mediated seems to be modulation of the *N*-acetyl-D-aspartate receptor-mediated calcium influx—a pathogenetically highly relevant process involved in neuronal death in neurodegenerative pathologies like Alzheimer's disease, Parkinson's disease, and Huntington's chorea (Nonaka et al. 1998).

Beyond these well-described cellular effects of lithium, animal and human studies have yielded other interesting cellular and clinical findings that raise hopes that lithium might become a therapeutic option in the treatment of neurodegenerative disorders like Parkinson's and Alzheimer's disease (Vo et al. 2015). For example, recent reports suggest a positive influence of lithium on the deposit of α-synuclein protein and β-amyloid protein—hallmarks of Parkinson's and Alzheimer's disease pathology (Hampel et al. 2009; Forlenza et al. 2014; Vo et al. 2015).

9.2.1 Neuroprotective and Cognitive Aspects of Lithium in Bipolar Disorder

Experimental and clinical findings illustrate that lithium displays both neuroprotective and neurotoxic effects, with the mechanism of action depending on the specific brain structure (Bauer et al. 2003; Rybakowski 2016). Lithium's influence on cognition in bipolar disorder patients continues to be debated (Pfennig et al. 2014). A meta-analysis demonstrated that lithium treatment is associated with a significant impairment of verbal learning and memory as well as impaired psychomotor performance during therapies of longer duration (Wingo et al. 2009). Overall, the most consistent pro-cognitive effect of lithium therapy appears to be that it lowers the risk of dementia in bipolar patients (Rybakowski 2016). There is evidence that lithium treatment for bipolar disorder is associated with a lower prevalence of Alzheimer's disease (Nunes et al. 2007). When considering the potential mechanisms involved in how lithium affects cognition, the correlation between the number of mood episodes and current cognitive deficits must be considered. In this context, an indirect cognitive effect of lithium by reducing mood episodes seems to be the most probable effect to date (Rybakowski 2016).

A consistently replicated body of evidence from cross-sectional and prospective studies demonstrates that lithium treatment is positively associated with brain gray matter volume. In one study, bipolar patients with no or limited lifetime lithium exposure had significantly lower hippocampal volumes than controls; in contrast, those with a comparable illness burden but over 2 years of lithium treatment showed hippocampal volumes similar to those of the healthy controls (Hajek et al. 2012b). Extended analysis of these data revealed that the association between lithium treatment and hippocampal volume seems to be independent of long-term treatment response and that it appears even in subjects experiencing episodes of bipolar disorder while on lithium (Hajek et al. 2014). The authors thus argue that lithium's neuroprotective effects on brain structure are not related to its efficacy in mood disorders and may therefore also apply to patients with neuropsychiatric illnesses other than bipolar disorder.

Similarly, in a study investigating the association between lithium treatment and brain *N*-acetylaspartate (NAA), a putative neuronal marker, the effects of lithium on prefrontal cortex NAA levels were compared in patients with bipolar disorder having received at least 2 years of ongoing lithium treatment (lithium group), with patients with a lifetime lithium exposure of under 3 months more than 2 years previously (non-Li group), and with healthy controls (Hajek et al. 2012a). Whereas patients with bipolar disorder, substantial illness burden and limited lifetime lithium exposure showed significantly lower prefrontal NAA levels than controls, lithium-treated patients with a similar illness burden revealed prefrontal NAA levels comparable to those of healthy controls (Hajek et al. 2012a). These findings also provide indirect support for lithium's neuroprotective effects and for the negative effects of illness burden on prefrontal NAA levels in patients with bipolar disorder.

In short, the clinical data support lithium as having neuroprotective properties, especially those attributed to reducing the prevalence of dementia in lithium-treated bipolar patients. At present, it is not known whether the reduction in dementia's prevalence represents a disorder-specific effect. Further studies are needed to answer this clinically relevant question. In this respect, lithium's narrow therapeutic index might be a major concern limiting future clinical research in this field. However, in light of the lack of neuroprotective treatment alternatives, clinical studies on high-risk populations would appear to be justified. In this context, the acceptable tolerability of lithium treatment in cognitively impaired patients is relevant (Macdonald et al. 2008; Hampel et al. 2009; Forlenza et al. 2011).

9.2.2 Lithium and Neuroprotection in Dementia

Due to its neuroprotective effects, lithium's potential use in treating and preventing neurodegenerative disorders has been evaluated using a variety of techniques. Its reported effects on β-amyloid and neurofibrillary tangles deposition have made it an especially promising therapeutic option for treating dementia (Phiel and Klein 2001; Donix and Bauer 2016). Experimental findings show that lithium influences the neuropathological hallmarks of Alzheimer's dementia. Preclinical data have

demonstrated lithium's effect on the overproduction of β-amyloid protein and on the process of hyperphosphorylation of tau protein (Zhang et al. 2011).

Lithium has not yet displayed beneficial effects on cognitive function in patients suffering from Alzheimer's disease under clinical conditions; however, certain study limitations might have influenced the results (Macdonald et al. 2008; Hampel et al. 2009). The tolerability and safety of lithium treatment in Alzheimer patients was not a limiting factor in those studies (Macdonald et al. 2008; Hampel et al. 2009). In a subset analysis of one of their study cohorts, lithium treatment was associated with elevated serum BDNF levels parallel to an improvement in cognitive performance (Leyhe et al. 2009).

Lithium was also tested in patients with amnestic mild cognitive impairment (aMCI) (Forlenza et al. 2011). In a randomized, double-blind trial, lithium treatment was associated with lower conversion rates to Alzheimer's disease, more consistent cognitive performance, and decreased levels of hyperphosphorylated tau protein (Forlenza et al. 2011). These clinical observations make lithium a reasonable medication candidate, especially in patients with the amnestic type of MCI (aMCI) associated with a higher risk of converting to dementia.

In summary, no clear conclusions can be drawn from the latest data on lithium's efficacy in treating Alzheimer's disease and aMCI patients. Despite the paucity of evidence, lithium use in aMCI patients seems to be promising, but larger clinical trials are urgently needed to evaluate its ability to preserve cognitive function and to prevent conversion from aMCI to Alzheimer's disease.

9.3 Lithium in Other Central Nervous System Disorders (CNS)

9.3.1 Huntington's Disease (HD)

The neuroprotective potential of lithium in HD is probably mediated via anti-apoptotic effects and the stimulation of proliferating neuronal and astroglial progenitor cells (De-Maw and Priller 2006). In animal studies, lithium treatment reduced striatal neurodegeneration (Lauterbach 2013). Lithium's clinical effects on HD were described as reducing chorea and improving voluntary movements (De-Maw and Priller 2006). A recent highly promising case series demonstrated that lithium seems able to halt the progression of chorea and dementia in HD patients (Danivas et al. 2013). However, its use in HD has generated contradictory results overall. At present, there is not yet a valid justification for lithium's off-label use for HD.

9.3.2 Amyotrophic Lateral Sclerosis (ALS)

The relevant neuroprotective mechanisms mediating lithium's beneficial clinical effects in ALS have been reviewed recently (Forlenza et al. 2014). Those that appear

to be most essential are lithium's capacity to induce the sprouting of pyramidal neurons in the corticospinal tract, the induction of synaptogenesis, the enhancement of neurotrophic responses, and the stimulation of autophagy (Forlenza et al. 2014). Lithium's use in ALS has been shown to retard disease progression under clinical conditions (Fornai et al. 2008). Recently, findings from the "lithium carbonate in amyotrophic lateral sclerosis trial" (LiCALS), a randomized, multicenter, double-blind, and placebo-controlled study, dampened hopes by showing that lithium has no beneficial effects on survival in ALS patients (UKMND-LiCALS Study Group et al. 2013).

In summary, recent studies have tempered the optimism resulting from promising preclinical and clinical data and from animal studies examining lithium's use in ALS. Against the background of contradictory study results, the disease-modifying qualities of lithium in treating ALS remain unclear.

9.3.3 Parkinson's Disease

Lithium has been studied in the management of L-dopa side effects like the "on-off" phenomenon and L-dopa-induced hyperkinesias (De-Maw and Priller 2006). Clinical research studies addressing lithium's beneficial effects on Parkinson's disease have so far been inconsistent. Experimental studies have suggested the prevention of striatal dopamine receptor desensitization, but this observation could not be transferred into measurable clinical effects (De-Maw and Priller 2006). Beyond that, lithium is assumed to protect against neuronal apoptosis in Parkinson's disease (Forlenza et al. 2014). When considering the investigation of lithium's beneficial effects on PD, one must keep the risk of lithium-induced parkinsonism and the potential for lithium-induced tremor in mind.

9.3.4 Cluster Headache

Lithium's prophylactic effects in cluster headache have been studied extensively. The amelioration of chronic cluster headaches has been reported, but study results are contradictory (Evers 2010). According to expert opinion, although the evidence for using lithium in this clinical condition is limited, it is more convincing in chronic cluster headache than in the episodic course (Evers 2010). Under controlled conditions, lithium demonstrated efficacy equal to the well-established first-line treatment of verapamil in chronic cluster headache. Despite the absence of clinical evidence, lithium is widely used in this condition (Bschor et al. 2006). In addition to its proven clinical efficacy, the rapid onset of prophylactic effects makes lithium a potent therapeutic option for chronic cluster headaches. Another recent retrospective study evaluated lithium's efficacy in preventing episodic cluster headache, demonstrating a significant reduction in attack frequency within 2 weeks of beginning treatment and providing evidence of lithium's capacity to modify the episodic form of cluster headache (Stochino et al. 2012).

9.4 Beyond Mood Disorders: Other Psychiatric Indications for Using Lithium

9.4.1 Schizophrenia and Schizoaffective Disorder

Lithium's manifold pharmacological effects suggest its use in various non-approved psychiatric indications. Research data exist on lithium's therapeutic effects in schizophrenia and schizoaffective disorder both as monotherapy and as add-on therapy accompanying antipsychotics (Baethge and Simhandl 2006). To date, however, there is no solid evidence that justifies lithium's use in monotherapy for patients suffering from schizophrenia (Leucht et al. 2015). The evidence is lacking as well on its capacity to augment antipsychotics in schizophrenia. Some clinical researchers maintain that affective symptoms, previous mood episodes, and a positive family history for mood disorders predict beneficial effects of lithium in schizophrenic patients. In this context, the accuracy of diagnostically differentiating between schizophrenia and schizoaffective disorder seems especially relevant. Current recommendations are for testing lithium's antipsychotic effects in schizophrenic patients without affective symptoms to evaluate the isolated lithium effect on genuine schizophrenic symptoms (Leucht et al. 2015).

9.4.2 Obsessive-Compulsive Disorder and Pathological Gambling

Lithium has also been tested as an adjuvant medication in obsessive-compulsive disorder (McDougie et al. 1991; Pigott et al. 1991). It revealed no clinically relevant effect on obsessive-compulsive symptoms in lithium-augmented patients in a controlled study with 16 patients on stable medication with clomipramine for at least 6 months (Pigott et al. 1991). In another controlled trial, lithium demonstrated no relevant beneficial effects as an augmenting regimen in fluvoxamine-refractory obsessive-compulsive disorder patients (McDougie et al. 1991).

In summary, there is currently minimal evidence that lithium reduces obsessive-compulsive symptoms when prescribed adjunctively. Moreover, lithium augmentation in a sertraline-refractory patient with obsessive-compulsive disorder led to the exacerbation of clinical symptoms. In pathological gambling, lithium plus valproate demonstrated statistically significant improvement in a double-blind, placebo-controlled trial (Pallanti et al. 2002). Further studies in this area are needed.

9.5 Administering Lithium in Nonpsychiatric Disorders

Lithium has been studied as a treatment for a variety of medical disorders, but most of the trials have been small or uncontrolled.

9.5.1 Hyperthyroidism

Lithium interferes with the synthesis and release of thyroid hormones at various sites by reducing iodine uptake into the thyroid gland in vivo and in vitro, inhibiting the conversion from tetraiodothyronine (T4) to triiodothyronine (T3) and retarding the release of thyroid hormones from the thyroid gland (Boccetta and Loviselli 2006). Lithium's use in thyrotoxicosis became a potential therapy thanks to these thyroid-suppressing effects (Papi et al. 2014). In this context, 300 mg of lithium carbonate every 6–8 h inhibits colloid proteolysis and is used as an alternative to inorganic iodine, helping to decrease the secretion of pre-formed thyroid hormones (Papi et al. 2014). Lithium can be an alternative in treating thyrotoxic storm, especially in patients not tolerating or not responding to thioamides. Furthermore, lithium has been suggested as an adjunct therapy in the therapy of hyperthyroidism with radioiodine (Lazarus 2009).

9.5.2 Hematological Indications

Lithium exerts a range of effects on peripheral blood cells, hematopoietic stem cells, and growth factor production. These effects include blood cell formation, particularly granulocyte and platelet production, that may have clinical indications under special circumstances. Specifically, lithium increases both granulopoiesis and megakaryocytopoiesis in vivo and in vitro at the identical concentrations at which it reduces erythropoiesis (Inayat and Gallichio 2006). Lithium increases colony-stimulating factor production, the molecules essential for the sustained proliferation and differentiation of various classes of hematopoietic progenitors. Lithium also stimulates proliferation of the pluripotent stem cell. Moreover, it influences the production of molecules that directly stimulate the proliferation of progenitor stem cells responsible for developing specific hematopoietic cell lineages. Lithium can thus be characterized as promoting both direct and indirect effects on the cell proliferation responsible for hematopoiesis development (Inayat and Gallichio 2006).

Lithium effects on blood cell production involve mechanisms responsible for cation transport across the cell membrane. This evidence demonstrates that transport processes play a key role in the mechanism responsible for hematopoietic cellular proliferation and differentiation. This area of research requires further study to properly evaluate how these pathways influence normal and diseased states.

The administration of lithium leads to neutrophilia. The increased production of granulocytes also influences the functional activities of these cells. As a general rule, lithium administration is associated with increasing the activity of neutrophils in combating infections; lithium therefore effectively increases both the number of phagocytes and their formation. Mechanistically speaking, lithium promotes granulocyte function via its ability to inhibit adenyl cyclase activity. Activation of the enzyme increases cyclic AMP, which limits granulocyte function, an effect reversed by lithium. Lithium increases granulocyte numbers not only when their production is faulty or inadequate but also in conditions where neutrophil function is

insufficient (Inayat and Gallichio 2006). Lithium's potential clinical use in these hematological indications should be restricted to specialists in hematology.

9.5.3 Herpes Simplex

Lithium has demonstrated antiviral effects by suppressing DNA-virus replication via competitively inhibiting magnesium as a cofactor in DNA-synthesizing enzymes. In addition to these antiviral effects, lithium's general immunomodulatory capacities and indirect effect via mood stabilization (followed by stress reduction) appear to be promising. Clinical observations suggest a lithium-mediated reduction in the frequency of recurrent labial herpes reactivation (Rybakowski 2000; Bschor et al. 2006).

9.5.4 Seborrheic Dermatitis

The topical use of lithium in seborrheic dermatitis is associated with beneficial effects regarding symptom categories such as burning and dryness and even occasionally inducing complete remission (Dreno et al. 2003). The use of topical lithium in a placebo-controlled trial revealed its significant superiority regarding complete remission rates; lithium appeared more effective than ketoconazole in achieving complete remission (Dreno et al. 2003). The mechanism by which lithium mediates this therapeutic effect is not well understood. Experimental data suggest a dose-dependent immunomodulatory effect leading to enhanced anti-inflammatory immune responses (Ballanger et al. 2008). In this context, any additional lithium effect is assumed to be of pathogenetic relevance—the modification of arachidonic acid metabolism (Ballanger et al. 2008). In summary, these clinical research results underline lithium's immunomodulatory effects.

9.5.5 Other Medical Conditions

Lithium has been studied in various other clinical conditions, demonstrating more or less efficacy. Because of the lack of evidence and clinical relevance, such potential indications are summarized below (Bschor et al. 2006) (Table 9.1).

Table 9.1 Overview of biological and clinical effects of lithium in nonpsychiatric conditions

Indication	Biological effects	Clinical effects
CNS disorders		
Huntington's disease	Neurotrophic effects; anti-apoptotic effects; stimulation of proliferating neuronal and astroglial progenitor cells	Reduction in chorea, improvement in voluntary movements, reports of nonprogression of chorea and dementia
Amyotrophic lateral sclerosis	Induction of synaptogenesis and sprouting of pyramidal neurons in corticospinal tract; enhancement of neurotrophic responses; stimulation of autophagy	Reports of decelerating disease progression, no effects on overall survival
Parkinson's disease	Prevention of striatal dopamine receptor desensitization	No beneficial clinical effects
Cluster headache		Good clinical effects in chronic and episodic form
Migraine		Mostly negative results, positive results for cyclic migraine
Epilepsy		Reduction in seizure frequency in case report and series, increase in seizure frequency in temporal lobe epilepsy, use with caution
Spasmodic torticollis		No effect
Hypnic headache		Positive results from case reports
Kleine-Levin syndrome (KLS, periodic hypersomnia)		Positive effects in case reports and a case series
Other medical conditions		
Cancer (general)	Inhibition of malignant cell lines, but also stimulation of certain malignant cell lines	
Thyroid cancer		No beneficial effects adjunctive to radioiodine treatment
Leukopenia (e.g., induced by cancer treatment)	Increases both granulopoiesis and megakaryocytopoiesis; increases colony-stimulating factor production; stimulates proliferation of the pluripotent stem cell	Improvement in leukopenia, no impact on overall survival, worsening of survival in patients with cardiovascular diseases
Human immunodeficiency virus (HIV)	Antiviral activity in in vitro and animal studies	No clear effects on course of HIV infection and AIDS

(continued)

Table 9.1 (continued)

Indication	Biological effects	Clinical effects
Bone marrow transplantation	In animal studies: positive effects when bone marrow donors were treated with lithium	
Meniere's disease		No effect
Hyperthyroidism	Inhibition of synthesis and release of thyroid hormones by reducing iodine uptake into the thyroid gland	Effective in thyrotoxicosis, but obsolete
Herpes simplex infection	Antiviral effects by suppressing DNA-virus replication via competitively inhibiting magnesium as a cofactor in DNA-synthesizing enzymes	Direct and indirect antiviral effects in humans
Seborrheic dermatitis		Good clinical effects
SIADH (syndrome of inappropriate antidiuretic hormone secretion)		Possibly useful, but cannot be recommended
Asthma		Slightly positive effect

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Lithium During Pregnancy and in the Postpartum Period

10

10.1 Introduction

Managing bipolar disorder during pregnancy and in the postpartum period is among the most difficult areas in psychopharmacology. The interindividual differences in course and treatment responses across women make for complex risk/benefit ratios for all strategies considered. Risks of treating and not treating must both be considered, requiring more intensive discussions than for any other clinical decision. Before reviewing the effects of lithium during and following pregnancy, some general issues surrounding pregnancy and birth control as well as the natural history of bipolar disorder during these times must be addressed.

When possible, management of pregnancy-related issues should be discussed with the woman (and the woman's partner, if present) before pregnancy so that the various strategies can be discussed and considered in a non time-pressured manner. Effective methods of birth control should also be discussed at this time. Of course, this is not always possible. Women (and men) in general, and bipolar women specifically, are not always meticulous about birth control. In bipolar women, impulsivity—due to breakthrough manias/hypomanias, comorbid drug/alcohol abuse, or personality issues—makes sexual activity without effective birth control common. It is estimated that over 50 % of pregnancies are inadvertent (Llewellyn et al. 1998). For bipolar women who are taking maintenance medication, this inherently results in some medication exposure to the fetus early in pregnancy given the delay in pregnancy confirmation, especially when it is unplanned. Additionally, early (i.e., prepregnancy) discussion should also include not only a detailed review of the potential effects of psychotropic medications but of health habits that have a direct effect on pregnancy/fetal outcome such as smoking, obesity, substance abuse, prenatal vitamins, and so forth.

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10.2 Course of Bipolar Disorder During Pregnancy and the Postpartum Period

In contrast to earlier thinking, pregnancy is not a time of unusual good mental health for bipolar women. Greater mood stability was, in the past, thought to be due to the combination of positive feelings about the pregnancy and of the effects of the higher levels of sex hormones during this period that allegedly gave rise to mood stability. Unfortunately, the majority of the more recent studies have consistently refuted the myth of greater mental health during pregnancy. In both unipolar and bipolar women, risks of mood episodes are substantial during pregnancy with higher relapse for bipolar vs. unipolar women (Viguera et al. 2000, 2007, 2011; Cohen et al. 2006). The risk extends across all three trimesters. In bipolar women, the first trimester confers the highest risk. This may reflect both the natural history of bipolar disorder and the effect of sudden discontinuation of a mood stabilizer when the pregnancy was unplanned and the mood stabilizer is stopped suddenly rather than tapered. In the best prospective study, depressive relapses dominated the clinical picture of bipolar disorder I and II women during pregnancy. This was especially true for bipolar II women for whom 89 % of relapses were depressive (Viguera et al. 2007). Similar findings were described in a large, recent study in which 23 % of bipolar women had a mood episode during pregnancy with rates similar between bipolar I and bipolar II women (25 % vs. 20 %, respectively). Here too, depressive episodes were more common than manic/hypomanic episodes, especially for bipolar II women (Viguera et al. 2011).

Bipolar women who discontinue their mood stabilizer either just before becoming pregnant or during the first trimester are at 2.3 times higher risk for relapse during pregnancy compared to those who continue mood stabilizer treatment (Viguera et al. 2007). Also, consistent with data from a nonpregnant bipolar population, women who discontinued any mood stabilizer (like lithium) suddenly relapsed far faster than those who tapered their mood stabilizer gradually over at least 15 days.

Examining a cohort of women on lithium specifically who either stopped treatment during the 6 weeks after conception or continued treatment throughout the pregnancy showed similar findings of markedly higher relapse in those who discontinued treatment (Viguera et al. 2000). Relapse rates were similar for pregnant women who discontinued lithium compared to an age-matched group who were not pregnant and discontinued lithium, suggesting no protective effect of pregnancy when lithium is discontinued. Similar to other studies, sudden discontinuation of lithium resulted in earlier relapses compared to those who tapered lithium more gradually (Viguera et al. 2000).

Rates of postpartum mood episodes in bipolar women far exceed the already substantial rates during pregnancy with a recent study estimating a 3.5 greater risk postpartum than during pregnancy (Viguera et al. 2011). Postpartum episodes tend to occur earlier for bipolar I women compared to women with bipolar II disorder or recurrent major depression (Di Florio et al. 2013) with most episodes occurring within 4 weeks of delivery (Harlow et al. 2007). Bipolar women who have had one hospitalized mood episode postpartum are at higher risk to have a postpartum episode in subsequent pregnancies.

10.3 Potential Effects of Lithium in Pregnancy

In evaluating the potential negative effects of lithium on fetuses/infants, two potential confounding factors must be considered. First, the base rate of these abnormalities must always be considered. As the most common example, the base rate of fetal malformations in healthy women not taking medications is 2–4 % (Stewart 2011). Second, the disorder for which the medication is being prescribed may have associations with negative pregnancy/birth outcomes. Confounding the question is the less than optimal health habits of many bipolar women which have clear adverse effects on pregnancy such as cigarette smoking, excessive alcohol intake, and/or illicit drug use. Similarly, the effects of depression during pregnancy in bipolar (or nonbipolar women) have not been systematically studied. Here too, poor health habits such as poor prenatal nutrition, excessive weight gain, and overuse of alcohol, tobacco, or other substances may all contribute to adverse outcomes. Theoretically, activation of the hypothalamic-pituitary-adrenal axis associated with depression may also have negative effects on fetal development and/or preterm delivery and low birth weight (Chaundron 2013). Consistent with these possibilities, in one study, bipolar disorder, whether treated or not, was associated with increased risk of caesarean delivery, preterm delivery, and head size abnormalities (Bodén et al. 2012). A specific effect of mania on pregnancy outcomes is simply unknown.

Given these considerations, with any individual woman, a causal relationship between an adverse outcome and the potential use of a medication—such as lithium—during pregnancy can never be ascertained definitively. In discussion with women, therefore, the potential risks of *not* treating and the negative effects of mood episodes during pregnancy on both the woman and fetus should be emphasized since these risks are less intuitive than the more obvious risks associated with taking medications.

As with any other psychotropic medication, lithium can potentially cause adverse effects during pregnancy in four different domains and are summarized in Table 10.1:

1. Effects related to pregnancy and its course: These would include risk of miscarriage, rates of preterm birth, and birth weight.
2. Fetal malformations: These are virtually always related to first trimester exposure.
3. Neonatal toxicity: Potential effects in this domain reflect third trimester exposure.
4. Developmental abnormalities, usually evident only months or years postpartum.

Table 10.1 Potential adverse effects of lithium in pregnancy/fetus

Pregnancy and its course	Preterm delivery Rate of miscarriages
Fetal malformations	Cardiovascular, especially Ebstein's anomaly
Neonatal toxicity	Floppy baby syndrome Hypothyroidism
Developmental abnormalities	None documented

10.3.1 Lithium: Effects Related to Pregnancy and Its Course

There is some evidence that lithium exposure is associated with prematurity, increased birth weight, and/or preterm delivery (Galbally et al. 2010). In the most recent study, exposure to lithium during pregnancy was associated with double the rate of miscarriage and somewhat higher rates of preterm delivery compared to bipolar pregnant women not treated with lithium (Diav-Citrin et al. 2014). As noted above, confounding effects such as poor health habits and the effects of bipolar disorder itself must always be considered.

10.3.2 Lithium and Fetal Malformations

Given that lithium easily crosses the placental barrier at close to 1:1 ratios compared to maternal concentrations, first trimester fetuses are exposed to substantial amounts of lithium. The overwhelming majority of studies regarding lithium's adverse events in pregnancy reflect concerns about teratogenicity, especially the development of the fetal heart. Of greatest concern is lithium's association with the development of Ebstein's anomaly, characterized by downward displacement of the tricuspid valve into the right ventricle and variable levels of right ventricular hypoplasia. In control populations, Ebstein's anomaly occurs in 1 in 20,000 births. In earlier studies, first trimester lithium-exposed infants showed alarming high rates of the Ebstein's anomaly. These high rates were assuredly due to the nature of reporting to birth registries, which tends to overestimate problems since clinicians are more likely to report abnormal outcomes than benign ones. A revised estimate using less biased methodology suggesting a more accurate rate of Ebstein's anomaly in lithium-exposed neonates is 1/1000, 20 times the base rate but still a rather low absolute rate (Cohen et al. 1994). In a recent meta-analysis, it was concluded that the odds of lithium exposure in Ebstein's anomaly were not significantly elevated (McKnight et al. 2012). Finally, in the most recent study, risks for persistent cardiovascular abnormalities in lithium-exposed neonates did not significantly differ from a control group of children born to bipolar women not exposed to lithium (Diav-Citrin et al. 2014). Of course, with a relatively rare adverse event such as Ebstein's anomaly and relatively small databases, to describe a difference as "not significantly different" does not equate to "not clinically relevant" (Bergink and Kushner 2014). Therefore, it is prudent for women receiving lithium during pregnancy to be monitored with fetal echocardiography and level 2 ultrasound treatment early in the second trimester. Of note, in contrast to other teratogenic defects such as neural tube defects, Ebstein's anomaly is surgically correctible.

10.3.3 Lithium and Neonatal Toxicity

Occasional cases of floppy baby syndrome, characterized by cyanosis and hypotonic muscle tone, have been described in neonates exposed to lithium in utero.

Other cases of neonatal hypothyroidism presumably due to lithium's effect on fetal thyroid function and nephrogenic diabetes insipidus (see Chap. 12 for details on both effects) have also been described. If hypothyroidism emerges during pregnancy, thyroid hormone supplementation is indicated.

10.3.4 Lithium and Developmental Abnormalities

No evidence of developmental abnormalities in infants exposed to lithium in utero has been shown, although no long-term studies exist (Yonkers et al. 2004).

10.4 Management of Lithium During Pregnancy and Delivery

Pregnancy alters the pharmacokinetics of lithium. During pregnancy, lithium clearance increases by 30–50 % due to increased renal blood flow, especially in the third trimester (Deligiannidis et al. 2014). Without dose adjustment, this results in a lower plasma lithium level, thereby placing the woman at risk for relapse. Therefore, lithium levels should be monitored regularly during pregnancy. During the last month of pregnancy, lithium levels should be checked every 1–2 weeks. Women must be encouraged to ensure that they drink sufficiently to stay well hydrated. At delivery, vascular volume decreases markedly as does lithium clearance, potentially resulting in lithium intoxication in the absence of dose adjustment. Management of lithium doses at the time of delivery is either to (1) stop lithium for 24–48 h and then restart at the prepregnancy dose or (2) decrease the lithium dose by 25–50 % in the week prior to expected delivery with the resumption of the prepregnancy dose following delivery.

10.5 Lithium, Breastfeeding, and the Postpartum Period

As described above, the highest risk period for a mood episode in a bipolar woman's life (and more than any period in a man's life) is the immediate postpartum time given that the question of effective preventive treatment starting at childbirth is critical. For those women for whom lithium is their effective mood stabilizer, lithium's safety during breastfeeding becomes the critical issue.

The advantages of breastfeeding are multiple, are well known, and include increased bonding with the infant, enhanced immune and gastrointestinal function in the neonate, and a decreased incidence of a number of diseases (Chaundron and Jefferson 2000). The primary disadvantage of breastfeeding for bipolar women is the sleep disruption associated with its use and the potential for mood stabilization secondary to the sleep disruption. Of course, breastfeeding does not need to be decided in a dichotomous way. It is feasible, for instance, for mothers to breastfeed during the day while having someone else bottle-feed the infant during the night,

thereby avoiding the sleep disruption while simultaneously achieving the psychological and biological benefits of the breastfeeding. For lithium specifically, it is also possible for the mother to take her daily dose just after the evening breastfeeding. With bottle-feeding during the night, the peak lithium levels will occur during the nonbreastfeeding time, thereby allowing the mother to be adequately treated while minimizing the lithium exposure in the neonate.

In general, lithium is secreted into breast milk with levels averaging just under half of the maternal serum levels, with marked variation across individuals. Infant serum levels are either the same as measured in the breast milk or somewhat less. Thus, infants exposed to lithium via breastfeeding are exposed to substantial amounts of lithium. A few case reports have demonstrated adverse outcomes in lithium-/breast milk-exposed neonates (Chaundron and Jefferson 2000). These adverse effects resolve if breastfeeding is discontinued. Symptoms of lithium toxicity in neonates include lethargy, hypotonia, cyanosis, and T wave changes on electrocardiogram (Altshuler and Kiriakos 2006). Because lithium levels are so sensitive to fluid status and given the immature renal function of neonates, the hydration status of neonates exposed to lithium via breast milk must be monitored carefully and regularly, especially in the situation of a viral or other febrile illness that might affect fluid intake.

The long-term effects of neonatal lithium exposure are unknown. Not surprisingly, given both the clear advantages of breastfeeding for bipolar women taking lithium and the equally clear concerns and disadvantages, clinical recommendations span the gamut from official contraindications to "use with caution" to encouraged use. Clearly, for any woman, the risks and benefits should be individually evaluated before a decision is made. This decision should be made well before the postpartum time so that there is sufficient time for reflection and for the construction of alternate plans.

For those women who have discontinued lithium during pregnancy and who want to resume lithium treatment postpartum, it should be restarted as soon after birth as is feasible with target doses and serum levels the same as prepregnancy. For those women who have continued lithium during pregnancy, the dose should be decreased due to changes in renal function as noted above with the same target of prepregnancy serum levels.

10.6 Clinical Decision-Making During Pregnancy for Women Taking Lithium

Given the information just reviewed, it must be obvious that no one clinical path will be the right one for all bipolar women considering becoming pregnant who are taking lithium as a mood stabilizer. Of course, women with milder bipolar disorders—mild bipolar II vs. bipolar I, with longer times between episodes, without comorbid psychiatric disorders, with strong social support in their lives, and who have no history of suicide attempts or frequent suicidal ideation—are better candidates to discontinue lithium or other mood stabilizers before pregnancy and not suffer a major mood episode.

Table 10.2 Practical recommendations for prescribing lithium during pregnancy and the postpartum period

Ensure fluid intake
Monitor lithium levels frequently, especially during third trimester
Fetal echocardiography in early second trimester TSH
At parturition, either D/C lithium for 48 h or decrease dose by 25–50 % for 1 week prior to anticipated birth
For neonates exposed to lithium in breast milk, ensure hydration
If lithium is discontinued during pregnancy, restart as soon as feasible postpartum with same target doses and levels as before pregnancy

When a woman discontinues lithium before conception, the amount of time without the mood stabilizers is completely variable ranging from a few weeks to many menstrual cycles before she becomes pregnant. When lithium is discontinued in a planned way, it should be tapered over at least 2 weeks and preferably 4 weeks to avoid discontinuation rebound symptoms (as noted above and discussed in more detail in Chap. 5). Some women want to consider discontinuing lithium only upon pregnancy confirmation. This is problematic since even first trimester exposure confers whatever risk there may be for fetal malformations. Another potential strategy in handling lithium around pregnancy is to discontinue the mood stabilizer before pregnancy and then restart it after the first trimester when organ formation is essentially complete. For those women who elect to utilize this strategy, lithium can either be restarted at the beginning of the second trimester or at the time of emerging/prodromal mood symptoms. In the latter circumstance, however, the assumption is that the patient will retain insight into the emerging symptoms and cooperate with medication resumption.

Bipolar women on lithium with more severe disorders as defined by symptom severity, episode frequency, psychiatric comorbidity, and treatment resistance should be urged to remain on preventive treatment during pregnancy given the high rate of episode recurrence without treatment. During pregnancy, lithium doses and serum levels should be decreased to the lowest level that is still therapeutic. It is unclear whether a divided dose regimen of lithium, which minimizes peak levels, decreases teratogenic risk.

Table 10.2 summarizes clinical recommendations for lithium's use during pregnancy and the postpartum period.

10.7 Other Mood Stabilizers During Pregnancy and Postpartum Periods

A detailed examination of mood stabilizers other than lithium and their risks and benefits during pregnancy is beyond the scope of this book. However, a brief review is needed since, in some situations, the question as to the relative risk for lithium vs. these other agents arises. In general, anticonvulsants are relatively teratogenic but with great differences across agents. Carbamazepine and valproate are

well-documented teratogens, associated with high rates—5–9 % for valproate—of teratogenic effects, especially neural tube defects like spina bifida (Yonkers et al. 2004). These effects are dose related and reflect exposure to the medications during the first month of pregnancy. Therefore, discontinuing either of these medications upon the confirmation of pregnancy is too late to alter the effect on neural tube development. Thus, if at all possible, these two medications should be avoided during the first trimester. Folate decreases neural tube defects generally, although it is less clear that it decreases valproate- and carbamazepine-related defects. Additionally, other milder anomalies, such as facial abnormalities, developmental delays, and fingernail hypoplasia, have also been described as consequences of carbamazepine and/or valproate exposure during pregnancy. In the EU, physicians are now advised not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant, or in girls unless other treatments are ineffective or not tolerated. The many difficulties associated with anticonvulsant exposure during pregnancy have led many practice guidelines to recommend lithium instead as a mood stabilizer if medications are required during pregnancy. Lamotrigine has a relatively benign safety profile when taken during pregnancy with overall rates of major fetal malformations similar to those exposed compared to the general population. From the extensive data derived from women with epilepsy, there is conflicted evidence that lamotrigine may be associated with slightly higher rates of cleft lip or cleft palate in infants exposed during the first trimester (Holmes et al. 2008). No behavioral problems or developmental delays have been associated so far in lamotrigine-exposed infants.

Antipsychotics, especially first-generation antipsychotics (FGAs), have a substantial naturalistic database due to their long use in schizophrenic pregnant women. FGAs seem rather benign in pregnancy with no specific teratogenic effects evident. Occasionally, a neonate exposed to FGAs in utero will exhibit transient extrapyramidal symptoms such as tremors and increased muscle tone restlessness/akathisia, symptoms that resolve within days of childbirth assuming that the neonate is not breastfeeding. No developmental delays have been described in infants exposed to FGAs in utero.

Although there is less experience with second-generation antipsychotics (SGAs), naturalistic evidence also demonstrates relative safety in pregnancy with these medications, with no increased risk of fetal malformations. Quetiapine crosses the placental barrier less efficiently compared to other antipsychotics, thereby suggesting less fetal exposure. Whether this translates to greater safety compared to other SGAs is unclear.

For both first- and second-generation antipsychotics, another consideration is the propensity, which differs across individual agents, for weight gain with the secondary risk during pregnancy of gestational diabetes.

A last option to consider in severely ill and/or treatment-resistant cases of mania or depression during pregnancy is ECT (Anderson and Reti 2009). The sparse data that exist suggests no evidence of teratogenic or neurodevelopmental effects. ECT has been occasionally associated with increased uterine contractions. The short-acting anesthetics used to facilitate ECT seem to be safe in pregnancy.

Safety concerns about mood stabilizers other than lithium during breastfeeding are unrelated to the risks during pregnancy. As examples, even though they are the most teratogenic of all mood stabilizers, valproate and carbamazepine are generally considered safe during breastfeeding (American Academy 2001). Breastfeeding infants have relatively low plasma levels of these medications with very few adverse events. Lamotrigine is secreted in breast milk with levels in the infant approximately 60 % of those of the mother. The only concern about lamotrigine and breastfeeding is the need to monitor for severe rash in the neonate.

Surprisingly few studies have examined the safety of either FGAs or SGAs during breastfeeding (Gentile 2008). No substantial risks are evident although some infants will have higher than expected levels and show side effects/toxicity.

The most common consideration for switching mood stabilizers before pregnancy would be with bipolar women stabilized on either carbamazepine or valproate who need to be on some maintenance treatment during pregnancy. In these situations, it makes sense to make the transition to either lithium, lamotrigine, or an antipsychotic before pregnancy. A good general strategy would be to add the second mood stabilizer to the first, gradually increase to a full dose and then to taper and discontinue the first anticonvulsant over at least 2 weeks.

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Practical Management of Lithium

11

11.1 Introduction

As outlined in this book in detail, lithium has unique properties as an effective mood stabilizer as well as demonstrating anti-suicidal and antidepressant effects. Despite the considerable success achieved by lithium, it remains a medication that is, compared with most psychotropic medications, more difficult to handle, largely due to its narrow therapeutic index. Together with concerns about its tolerability and long-term risks (Chap. 12), this is one of the reasons lithium is underutilized in clinical practice worldwide. There is also the perception that the frequent and reliable monitoring of lithium plasma concentrations is difficult. However, when used properly, lithium is generally well tolerated and not too complicated to administer. This chapter is dedicated to providing practical recommendations for the safe use of lithium in clinical practice.

11.2 Selection of Patients and Indications

Lithium is the mood stabilizer par excellence for the treatment of bipolar disorder. Lithium therapy provides several benefits: It stabilizes severe mood fluctuations, prevents mood episodes of both poles, and exerts acute antimanic effects. It is also used to decrease aggressive and disruptive behavior beyond mood disorders in other patient groups (e.g., aggressive behavior disorders, see Chap. 8; Müller-Oerlinghausen and Lewitzka 2010). Lithium is also indicated as monotherapy to treat acute episodes of unipolar depression and as maintenance treatment to prevent the recurrence of unipolar depressive episodes (Bauer et al. 2010; Nelson et al. 2014; Chap. 7). Furthermore, lithium has been demonstrated to prevent suicides in the long-term treatment of mood disorders, an effect that is probably independent of its mood-stabilizing effects (Lewitzka et al. 2015; Chap. 8).

It is often difficult during the early course of illness to evaluate the weight of benefits and risks of lithium treatment in individual cases. However, criteria have been

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developed to help physicians and patients decide whether lithium therapy should be initiated. More detailed information about the different indications of lithium in long-term treatment in patients with mood disorders is provided in Chap. 5.

Responders to lithium prophylaxis can be reliably identified beforehand by a comprehensive clinical assessment. It is important to consider not just a certain symptom presentation at one time but the patient's broad clinical profile as well including family history, early development, and comorbidity (Grof 2006). To date, the strongest clinical predictors include a family history of bipolar disorder, an episodically remitting clinical course, low rates of comorbidity, and typical clinical presentation of bipolar disorder (Kleindienst et al. 2005; see Chap. 5).

In case the clinical profile is not fully known or detailed information for a rational decision is missing, the patient should still be carefully considered for lithium. If lithium therapy is started, it should be time-limited until more information becomes available or the clinical course reveals the patient's response. In case of frequent recurrences during lithium maintenance treatment, or when the potential benefit is questionable, alternatives to lithium should be discussed (Chap. 13).

11.3 Contraindications for Lithium Therapy

An absolute contraindication exists when lithium treatment is judged to present a risk of such importance that the expected potential benefit of treatment can under no circumstances justify the risk. Relative contraindications exist if, before starting treatment or once it has been initiated, the patient exhibits symptoms of physical or mental illness that would imply that lithium therapy could worsen the condition. Table 11.1 provides relative and absolute contraindications (including information

Table 11.1 Relative and absolute contraindications for lithium treatment

	Relative	Absolute	Why?
Renal	Decreased glomerular filtration rate, tubular disorders	Acute renal failure	Can lead to a modest decline in renal function which may lead to nephrogenic diabetes insipidus (frequent); Chronic lithium nephropathy (rare); nephrotic syndrome (very rare)
Cardiovascular	Cardiac rhythm disorders	Acute heart attack	Can lead to nonspecific alteration of repolarization/dysfunction of impulse generation and conduction
Endocrine	Addison's disease	–	Endocrine disease can be aggravated by lithium
Dermatologic	Psoriasis	–	Can lead to a worsening of psoriasis symptoms
Neurologic	Cerebellar disorders, myasthenia gravis	–	Lithium can lead to ataxia and muscle weakness
Hematologic	Myeloid leukemia	–	Can lead to mild leukocytosis
Gynecologic	Pregnancy, first trimester	–	Increased risk of congestive heart failure
General	Low-sodium diet, anesthesia/surgery	–	Can lead to toxic serum levels

on the suggested mechanism) that would rule out lithium treatment. It is important to note that in general, a prior history of thyroid disease does not contraindicate lithium treatment.

There are only two absolute contraindications: acute renal failure and acute myocardial infarction. Another rather rare contraindication known is hypersensitivity to lithium. All other medical conditions such as cardiac disease or heart failure; renal impairment; low body sodium levels, including dehydrated patients or those on low-sodium diets; Addison's disease, and Brugada syndrome (including a family history of Brugada syndrome, a potentially life-threatening heart rhythm disorder) present relative contraindications. If the psychiatric indication for lithium is very severe in conjunction with such a medical condition, and if such a patient fails to respond to other mood stabilizer medications, lithium treatment may be started with extreme caution, including daily serum lithium measurements and adjustment to the lowest but effective doses tolerated by that patient. In such cases, hospitalization of the patient is recommended if possible.

Particular caution is necessary in case of clinical conditions known to potentially negatively interfere with lithium therapy, e.g., hypertension, (vascular) dementia, epilepsy, or Parkinson's disease. Occasionally only a lower-than-usual lithium level is tolerated in patients with these conditions (Berghöfer et al. 2006).

11.4 Drug Interactions with Lithium

Medications that alter serum lithium concentrations must be prescribed with great care and lithium carefully monitored. The lithium dosage and dosages of other medication(s) need to be adjusted. Co-medications associated with potentially hazardous (and those with less significant) interactions are displayed in Tables 11.2 and 11.3.

Table 11.2 Co-medication with potentially hazardous interactions

Analgesics (NSAIDs), e.g., diclofenac, ibuprofen, aspirin	Excretion of lithium reduced; increased risk of toxicity; avoid concomitant use; note: paracetamol is safer to use with lithium
Angiotensin-II antagonists, e.g., losartan ACE inhibitors, e.g., enalapril	Excretion reduced; increased plasma concentration; may cause toxicity; monitor closely for signs of lithium toxicity and consider taking lithium levels; be alert for the need to reduce the lithium dose (possibly by one third to half)
Antiarrhythmics, e.g., amiodarone	Risk of ventricular arrhythmias; avoid concomitant use
Diuretics (thiazides, potassium-sparing and loop diuretics)	Excretion reduced; increased plasma concentration and risk of toxicity; loop diuretics are safer than thiazides
Methyldopa	Neurotoxicity may occur without increasing plasma concentration of lithium; avoid concurrent use whenever possible
Sertindole (also see antipsychotics, Table 11.3)	Increases risk of ventricular arrhythmias; avoid concomitant use

Table 11.3 Co-medication with less significant interactions

Antidepressants, e.g., SSRIs, tricyclics, venlafaxine	Increased serotonergic effects seen and an increased risk of CNS effects as well as risk of lithium toxicity reported; all can increase lithium toxicity without affecting lithium levels
Antipsychotics	Increased risk of extrapyramidal side effects and possible neurotoxicity; monitor for risk of QTc prolongation
Antiepileptics, e.g., carbamazepine, phenytoin, topiramate	Neurotoxicity may occur without increased lithium plasma concentrations
Antacids, e.g., sodium bicarbonate	Excretion increased; reduced plasma concentration
Calcium channel blockers	Neurotoxicity may occur with diltiazem or verapamil without increasing the plasma concentration of lithium
Muscle relaxants	Lithium enhances the effect of muscle relaxants; hyperkinesis caused by lithium is aggravated by baclofen
Parasympathomimetics	Lithium antagonizes the effects of neostigmine and pyridostigmine
Theophylline	Increased excretion of lithium; reduced plasma lithium concentration; depressive and manic relapse may occur if the dosage of lithium is not raised when theophylline is given; lithium levels should be monitored if theophylline (or aminophylline) is stopped, started, or altered
Acetazolamide	Excretion of lithium is reduced
Metronidazole	Increased risk of lithium toxicity

11.5 Before Starting Lithium Treatment

The most important first step is to provide clear and useful information on lithium therapy both to the patients and their caregivers and relatives. It is well known that psychological interventions have proven to be helpful in enhancing adherence in lithium-treated patients (Rosa et al. 2007). Patients and their relatives often have negative, irrational, and fearful attitudes toward lithium therapy. Establishing a stable and enduring relationship between patient and physician is the best prerequisite for safe and effective lithium therapy.

Before the patient starts lithium therapy, a full history should be taken and a comprehensive medical evaluation carried out. A general physical examination (by either the psychiatrist or a primary care physician) should place emphasis on the neurological and the dermatological systems. Except in extraordinary circumstances, pregnancy should be considered a contraindication. Several laboratory tests should be performed before starting lithium therapy. In some settings, certain examinations are indicated (i.e., electrocardiogram [ECG] and ultrasound of the thyroid gland); blood pressure and heart rate should be measured. Furthermore, it is advisable to assess body weight, height, and neck size before starting treatment. Table 11.4 provides an overview of recommended examinations.

Table 11.4 Recommended tests and other investigations before and during lithium treatment (monitoring)

	Screening before starting lithium treatment	Monitoring during lithium treatment	
Organ/system	Parameter	Parameter	Time interval
Physical status	Physical/neurological status	Physical/neurological status	Annually
	Height		
	Weight	Weight	Annually
	Neck size[a]	Neck size[a]	Annually
Cardiovascular	Electrocardiogram (ECG)[a]	Electrocardiogram[a]	Annually
	Blood pressure	Blood pressure	Every 3–6 months
	Heart rate	Heart rate	Every 3–6 months
Renal	Serum creatinine	Serum creatinine	Every 3–9 months
	Creatinine clearance	Creatinine clearance	Every 3–9 months
	Glomerular filtration rate	Glomerular filtration rate	Every 3–9 months
Thyroid gland	Ultrasound of the thyroid gland[a]	Ultrasound of the thyroid gland[a]	Annually
	Triiodothyronine (T3)[a]	Triiodothyronine (T3)[a]	Every 6–12 months
	Thyroxine (T4)[a]	Thyroxine (T4)[a]	Every 6–12 months
	Thyroid-stimulating hormone (TSH)	Thyroid-stimulating hormone (TSH)	Every 6–12 months
Parathyroid gland	Parathyroid hormone	Parathyroid hormone	Annually
Blood count	White blood cell count[a]	White blood cell count	Every 6 months
	Red blood cell count[a]	Red blood cell count	Every 6 months
	Hemoglobin (Hb)[a]	Hemoglobin (Hb)	Every 6 months
	Hematocrit (Hk/Hct)[a]	Hematocrit (Hk/Hct)	Every 6 months
Electrolytes	Sodium	Sodium	Every 6 months
	Potassium	Potassium	Every 6 months
	Calcium	Calcium	Every 6 months
Metabolism	Fasting glucose level[a]	Fasting glucose level[a]	Annually
Other	Side effects from other medications	Side effects from other medications	Every visit

[a]Optional tests

Special attention must be given to the patient's renal function, as lithium can alter kidney function during long-term treatment (Severus and Bauer 2013). Measuring creatinine clearance (24 h urine collection) is recommended, as this

provides the most accurate glomerular filtration rate. If 24 h urine collection is not possible, measuring serum creatinine and potentially calculating the eGFR (estimated glomerular filtration rate) represent reasonable alternatives (Morriss and Benjamin 2008). The eGFR is usually provided directly by the laboratory.

The Cockcroft-Gault equation is generally used to calculate the GFR:

$$\text{Creatinine clearance}\left(\text{ml}/\text{min}\right)=\frac{\left(140-\text{age}\right)\times\text{body weight}\left(\text{kg}\right)}{\text{Serum creatinine}\left(\text{mg}/\text{dl}\right)\times 72}\left(\times 0.85\,\text{for females}\right)$$

11.6 How to Titrate Lithium?

Before starting lithium treatment, the type of formulation (tablet, capsule, liquid) and preparation (e.g., lithium carbonate, lithium sulfate, lithium citrate, lithium acetate) should be considered. The type of lithium salt being used is irrelevant from a practical perspective, as the lithium ion is the effective component. Because the amount of lithium released from different brands varies, it is recommended to stay with the same brand of lithium or to remeasure the lithium level and adapt the dosage if a brand change is necessary. Maintaining the same brand in the same patient is also advisable because lithium salts are completely absorbed from the gastrointestinal tract and absorption can be affected by how the preparation being taken is formulated.

A few older studies have compared the pharmacokinetics of different lithium formulations and demonstrated that the lithium citrate preparation has a pharmacokinetic profile that differs somewhat from that of lithium carbonate preparations; liquid lithium citrate was absorbed more rapidly than the solid form (Markar and Ascough 1991). However, the 12 and 24 h concentrations were the same regardless of which preparation had been used (Shelley and Silverstone 1986). Sustained slow-release formulations have lower peak plasma concentrations, resulting in fewer side effects for some patients. Lithium's half-life is about 24 h making once-daily dosing possible; however, from a clinical perspective, patients sometimes suffer fewer adverse effects when taking lithium twice daily. Clinicians using a once-daily dosage should also keep in mind that standardized 12 h levels will be higher for the same amount of lithium given once a day compared to divided doses (see also Chap. 4).

As lithium's therapeutic range is relatively small, its dosage must be carefully tailored to the individual patient (for an example see Table 11.5).

It is important to maintain stable plasma concentrations in each individual to achieve equilibrium between efficacy and potential side effects. Ignoring differences in the lithium content according to the type of preparation can lead to under- or overdosages of lithium. It is therefore best to express the lithium content as milligrams in the lithium tablet.

As food does not interfere with lithium absorption, no special advice is needed on whether the patient should take lithium before, during, or after a meal. However,

Table 11.5 Example for the titration of lithium carbonate (1 tablet = 450 mg [12.2 mEq/l])

	Morning	Lunch[a]	At bedtime
Day 1	0	0	½
Day 2	½	0	½
Day 3	½	0	½
Day 4	½	0	1

Continue until day 7

First lithium level measurement at day 5–7 (12 h after the last intake), depending on the result the dosage needs to be adjusted; usually it is recommended to take the highest amount of the dosages at night

[a]A few patients prefer to split the dosage two or three times daily

taking lithium with or after meals may minimize the gastrointestinal distress (e.g., nausea) that is sometimes seen early in lithium therapy temporarily. It is also important that patients take their medication with enough liquid.

The physician can begin therapy by administering 300–900 mg/day (8–24 mEq), preferably distributed over two daily doses, with the dose depending on age (lower in old age patients) and creatinine clearance. Clinical experience has generally shown that lithium is well tolerated when titrated within the first week up to 20–32 mEq (750–1200 mg) per day, but to avoid side effects, treatment should begin with a daily dose as low as possible and then increased until the optimal dose is attained. Faster dose titrations can be more easily achieved if the patient is hospitalized than with outpatients. Due to a lower glomerular filtration rate, especially in patients of low body weight and older patients (particularly women), in such individuals, a dose of 300–450 mg/day (8–12 mEq/day) often suffices.

After 5–7 days of lithium therapy, the lithium serum level should be measured 12 h (11–13 h is acceptable) after the last intake if a twice-daily regimen is being used. Lithium is often prescribed to be taken once daily in several countries. In these circumstances, the lithium level can be taken either in the morning or evening. However, evening dosing will allow the more convenient morning blood draw. In usually prescribed doses, the relationship between lithium dose and level is proportional. For example, if the lithium level is 0.4 mEq/l and the intended plasma concentration is 0.8 mEq/l, the daily dose should be doubled. Steady-state lithium concentrations can usually be achieved after 5 days of daily administration.

The time required before lithium achieves a satisfactory mood-stabilizing effect varies, whereas the antimanic and augmentation (antidepressant) effect often appears between 2 and 4 weeks. It can be difficult to achieve a clinical outcome that keeps the patient motivated to continue the treatment, as side effects may appear rather quickly and sooner than therapeutic effects. The clinician needs to arrive at an acceptable compromise with the patient while considering all of his or her individual circumstances. Patients are often willing to tolerate mild side effects rather than experience a new episode of their disorder. Methods for reducing side effects of lithium treatment are described in Chap. 12.

11.7 Therapeutic Lithium Level

The range of lithium serum levels generally recommended for maintenance treatment lies between 0.6 and 0.8 mEq/l. Levels up to 1.2 mEq/l are often needed in case of acute mania. Serum lithium concentrations below 0.5 mEq/l are rarely effective (Nierenberg et al. 2013; Nolen and Weisler 2013).

The optimum lithium level depends on age, sex, renal clearance, and the variance in the response to treatment. For example, younger patients (especially young men) may sometimes require levels up to 1.0 mEq/l for an acceptable maintenance outcome. The lithium level in elderly patients needs adjustment depending on efficacy and tolerability.

There is, of course, an increased risk for side effects with higher levels. However, an unsatisfactory response is often caused by the fact that no attempt had been made to attain slightly higher lithium levels in such patients. Levels above 1.0 mEq/l are rarely necessary for long-term (prophylactic) treatment. Figure 11.1 illustrates a

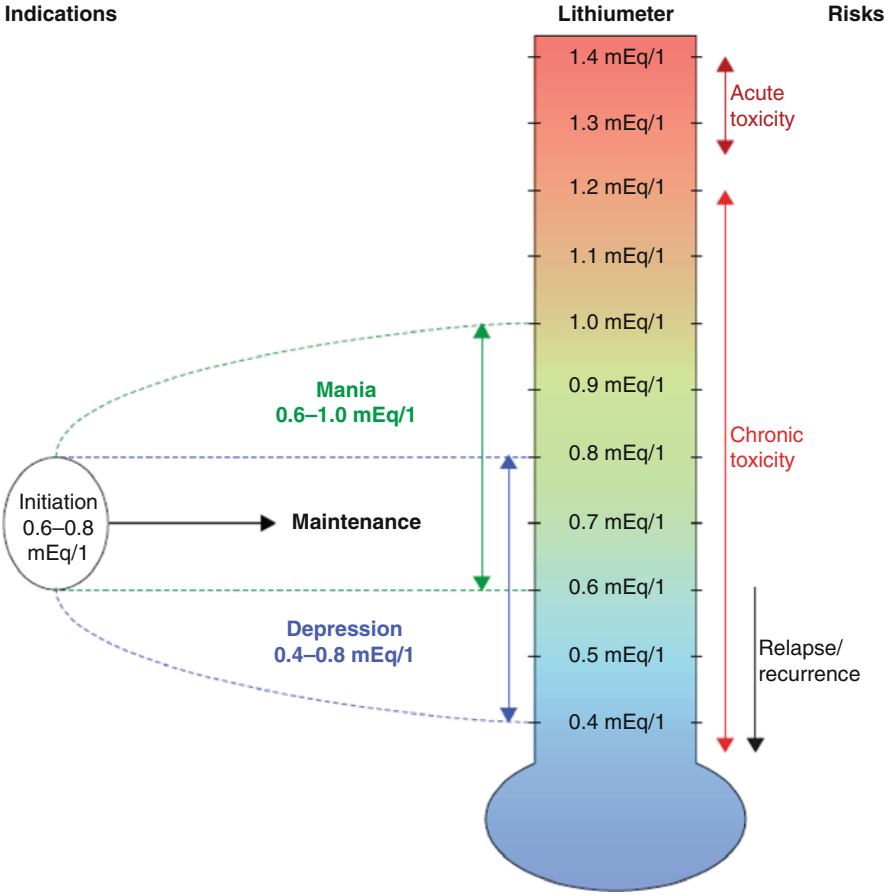

Fig. 11.1 The lithiumeter: indications and risks associated with lithium according to its blood levels (With permission from Malhi et al. 2012)

helpful tool (the so-called lithiumeter; Malhi et al. 2012) to determine the optimal lithium blood level considering the patient's current mood state and risks according to its blood levels.

Even if the same dose is being taken, the lithium level can vary intra- and inter-individually. Causes of this fluctuation are changes in the lithium absorption and hydration status (e.g., due to gastrointestinal infections, fever), co-medications, and changes in renal excretion (e.g., a low-sodium diet, intercurrent renal diseases). To improve patient adherence, it is better to have the patient take the lithium dose at about the same time every day; a few hours difference in intake time will not present a significant problem when considering its long elimination half-life.

11.8 Monitoring During Lithium Treatment

The need for regular monitoring is widely recognized, although several studies reported that it is often performed less frequently in clinical practice than is usually recommended by national practice guidelines (Kilbourne et al. 2007). A study by Paton et al. (2013) was designed to test an audit-based quality improvement program (QIP) addressing lithium prescribing and monitoring in the United Kingdom mental health services. They showed that participation in such a program was associated with improvements in achieving lithium monitoring, an important factor in outcome and safety.

Lithium level should be drawn 5–7 days after starting and 1 week after each dose change until stable levels have been achieved. The clinician should always aim for the minimum dose to achieve a therapeutic response. Older adults should be monitored more closely, as they have a higher risk of developing toxicity. Lower doses can sometimes be used in this population because older patients can develop symptoms of lithium toxicity at standard therapeutic levels. Table 11.4 provides an overview of recommended investigations during the long-term course.

Lithium can lead to a reduction in renal concentrating capacity and to a condition resembling diabetes insipidus. This has practical consequences, as patients with polyuria are at a higher risk of becoming dehydrated and subsequently developing lithium intoxication, especially when they fail to compensate by increasing their oral liquid intake. Since long-term renal damage is predicted by episodes of lithium toxicity, it is essential to avoid even low level lithium intoxication. Particular attention is required if patients taking lithium over the long term exhibit an abnormal estimated glomerular filtration rate (eGFR) (i.e., below 60 ml/min). Such an abnormality does not indicate renal damage unless there is a fall of >4 ml/min per year; thus, it is important to monitor serial eGFRs. If patients present a decreasing eGFR over time (below 60 ml/min), or any eGFR below 30 ml/min without acute dehydration, further renal tests and an immediate referral to a renal specialist are indicated. Of note, eGFR can be inaccurate in those aged below 18 years or above 70 years, and that patients of Afro-Caribbean origin require an adjusted formula.

As lithium is a thyroid-suppressing compound, patients often display increased basal TSH levels, which can trigger thyroid enlargement (goiter) (Bauer et al. 2007).

In case of euthyroid goiter, suppressive therapy with 50–100 mcg of L-thyroxine per day should be initiated.

It is also advisable to record lithium levels on a drug chart (and the patient's "lithium pass") with the date of the test, as well as in the clinical charts.

Lithium level and other related blood tests should be done more frequently than listed in Table 11.4 if signs appear of clinical deterioration and symptoms suggesting abnormal renal or thyroid function such as unexplained fatigue. Any situation associated with fluid loss such as fever, diarrhea, or vomiting can increase the lithium level. Patients should be informed that if such a situation arises, immediate lithium level monitoring is recommended.

Even closer monitoring may be necessary in patients with some comorbidities. For example, diuretics should be used cautiously in those with hypertension, and a low-salt diet is not recommended. It is a good idea to send the patient's general practitioner a copy (with the patient's consent) of his or her therapy plan including diagnosis, current blood test results, list of concomitant medications, and professional healthcare contact details. The brand, form, strength, and dosage of lithium should also be clearly stated in any correspondence. Of course, it is likewise helpful if the general practitioner provides other relevant medical information to the psychiatrist.

If the 12 h lithium plasma level exceeds 1.5 mEq/l, lithium administration should cease immediately, and a clinical assessment should be performed. In case of a persistently elevated lithium level (accompanied by other abnormal blood tests), referral to the hospital should be considered. Patients presenting levels >2.0 mEq/l clearly need to be monitored at the hospital.

11.9 Treating Lithium Intoxication

Lithium intoxication is usually preventable if the patient has been properly screened for lithium treatment, educated, monitored, and provided with the individually tailored dosage. Still, lithium intoxication is unfortunately not infrequent. Different subtypes of lithium intoxication have been described: acute, acute-on-chronic, and chronic forms, which differ in their symptomatology due to lithium's pharmacokinetic properties (Fig. 11.2). (Chapter 12 discusses the symptoms and risk factors for lithium toxicity.)

Treatment of lithium intoxication depends on the severity of the toxicity. First, with even the suspicion of lithium intoxication, lithium treatment should be suspended. A serum lithium level should be obtained (with care taken to note the time between the last lithium ingested and the time the level was drawn to ensure accurate interpretation). With mild, acute intoxication not requiring hospitalization, simply holding lithium doses until the toxic symptoms diminish should suffice. Exploring the etiology of the intoxication is also important in order to avoid future toxic episodes. With more severe toxicity, supportive care in the emergency room and/or intensive care unit may be required. Only if toxicity was due to an acute, very recent (few hours) overdose, ipecac syrup to induce vomiting, gastric lavage, or

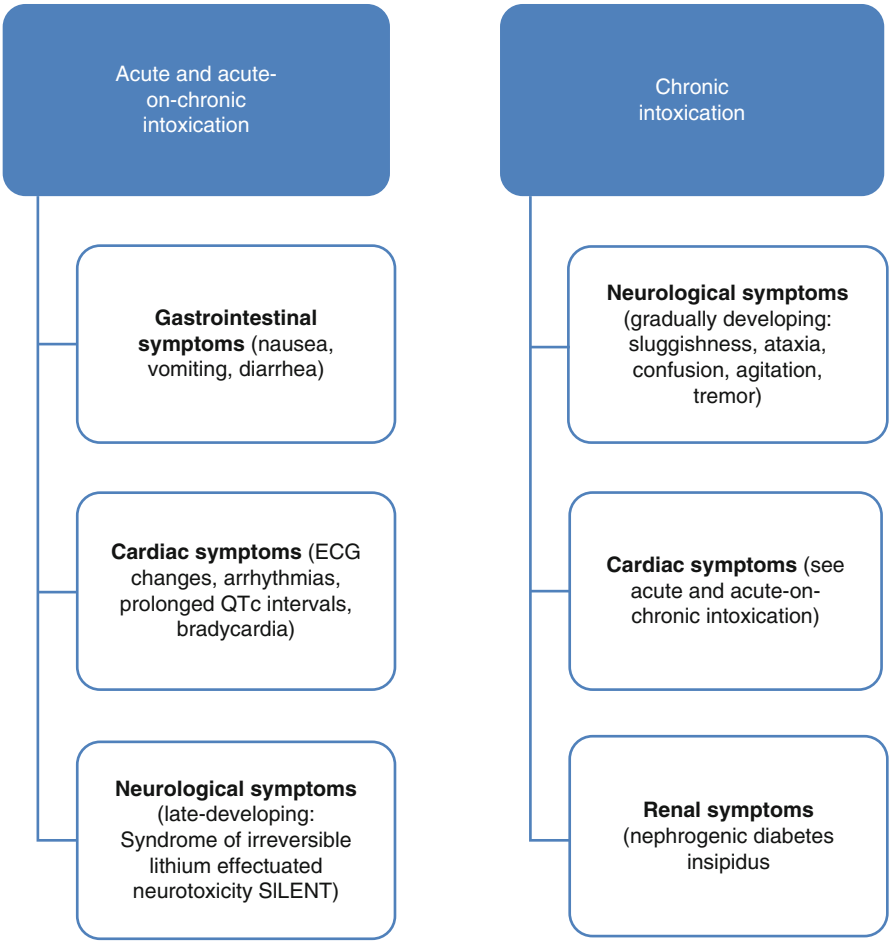

Fig. 11.2 Clinical signs and symptoms of acute and chronic lithium intoxication (With permission from Haussmann et al. 2015)

activated charcoal should be administered. Infusion of half normal to normal saline solution is often very helpful to enhance lithium diuresis. During this treatment, serum sodium and lithium levels should be checked regularly. With the more severe acute and chronic toxicities, hemodialysis (intensive care unit) should be instituted. Often, after a few dialysis treatments, lithium intoxication symptoms and lithium levels may raise again as intracellular lithium reenters the bloodstream.

The general approach to the severely lithium-intoxicated patient is similar to that used for other types of poisoning, namely, airway management (especially in patients with an altered mental status) and placement of a nasogastric tube and gastric lavage, especially when patients present shortly (few hours) after intoxication (Fig. 11.3). Lithium has proven to be one of the most readily dialyzable compounds.

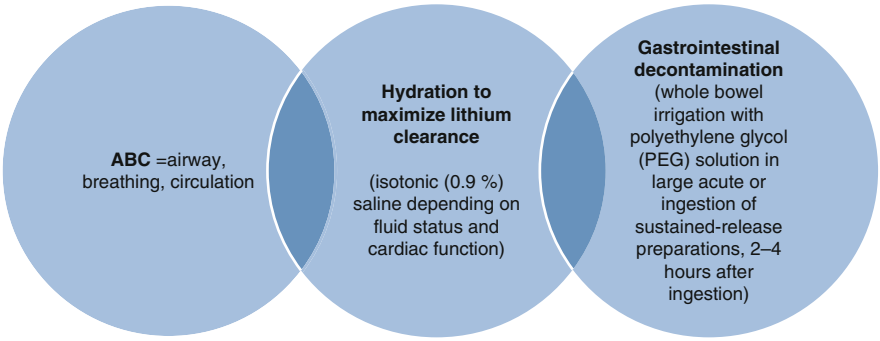

Fig. 11.3 General recommendations for treatment of lithium intoxication (With permission from Haussmann et al. 2015)

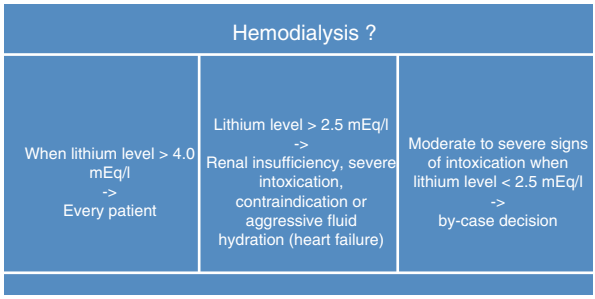

Fig. 11.4 Indications for hemodialysis in patients with lithium intoxication (With permission from Haussmann et al. 2015)

To date, there are no consistent recommendations regarding the initiation of hemodialysis in the lithium-intoxicated patient (Haussmann et al. 2015). In light of the latest evidence, hemodialysis should be conducted in any patient with lithium serum levels exceeding 4 mEq/l, regardless of their clinical status and the etiology of intoxication. If lithium levels are >2.5 mEq/l, hemodialysis should be initiated in any patient suffering from severe signs of lithium intoxication, when renal impairment is apparent, when the patient exhibits other conditions of limited lithium excretion, or when other illnesses (e.g., heart failure) could potentially deteriorate by extensive intravenous hydration (Fig. 11.4). Serial measurements of lithium levels are mandatory after hemodialysis has been initiated, as rebound phenomena are a major concern (due to re-equilibration from the extracellular sites). Lithium concentrations should initially be measured every 2–4 h to evaluate treatment efficacy until concentrations approach therapeutic levels. To control the rebound phenomenon, dialysis should be repeated if necessary until lithium levels remain below 1 mEq/l for 6–8 h after treatment (Haussmann et al. 2015).

With appropriate recognition and timely treatment, lithium toxicity is generally reversible. Two potential sequelae of lithium toxicity are worthy of concern: First, lithium toxicity episodes are predictive of later, more clinically relevant renal damage which may necessitate lithium discontinuation. Second, lithium intoxication

that lasts for days—usually because treatment was not instituted quickly enough—can result in permanent cerebellar damage with ataxia and cerebellar tremor as permanent long-term symptoms (Niethammer and Ford 2007).

11.10 How to Withdraw Lithium

When the risks and benefits of lithium therapy are assessed during the treatment course, patients and physicians may consider discontinuing lithium prophylaxis. Potential reasons to stop taking lithium are:

- Serious or intolerable side effects.
- Outcome of prophylactic, long-term treatment is inadequate.
- Lithium is no longer indicated (e.g., because of other intermediate diseases).
- Other circumstances such as pregnancy (lithium during pregnancy will be discussed separately in Chap. 10).

The patient's medical records and a mood diary/chart should be taken into account to determine whether the prophylaxis was a partial or complete success. Clinical experience has shown that it may take years to measure the full extent of lithium's efficacy of lithium therapy.

If lithium must be discontinued (especially after years of treatment), the dose should be gradually reduced over several months, as studies reveal that sudden discontinuation can trigger acute and severe relapses of manic, depressive, or schizoaffective episodes. Patients who failed to achieve complete stabilization while taking lithium or who present residual symptoms seem to have a particularly high risk for acute relapses. The longer the patient was on lithium, the longer the discontinuation period should last. The patient's psychiatric condition must be monitored more closely, while the lithium dosage is being reduced. If the patient remains stable over several months at a lower dose, the clinician can try to discontinue the treatment altogether, but if he or she deteriorates, the dose should be increased to its original level. Lithium must be discontinued in case of serious side effects. It is important to keep in mind that abruptly stopping the medication does not always trigger an immediate relapse (see also Chap. 5).

The clinician should be especially cautious when planning to terminate lithium therapy because of the withdrawal of the mood-stabilizing effect. Continuing lithium therapy can be discussed (from an anti-suicidal perspective) if the patient is burdened with a considerable suicide risk and the genetic (family) load or individual history might suggest its use; however, the continuation of lithium for its anti-suicidal effects must be clearly documented.

Should lithium be used as an augmentation strategy in unipolar depression and the patient responds, effective lithium add-on doses should be continued in combination with the antidepressant for at least 12 months after remission (probably even longer in those suffering from recurrent and difficult-to-treat, refractory depression) (Bauer et al. 2000).

11.11 Common Mistakes in Lithium Treatment

The authors of this book have observed a number of frequent errors made by physicians while prescribing lithium. Among these, the most common are (1) prescribing lithium in patients with ambiguous diagnoses, (2) stopping lithium therapy before the stabilization effect has been achieved (minimum 6 months), (3) not recognizing signs of (chronic) intoxication, (4) neglecting the anti-suicidal effect of lithium, or (5) a lack of attention to the recommended monitoring schedules (e.g., lab tests).

Lithium therapy tends to be more time consuming than other pharmacological strategies. Clinicians need to take the time to make correct diagnoses, obtain information, educate the patient, and initiate examinations and close monitoring. Nevertheless, lithium therapy is standard treatment, both at specialized lithium or mood disorder clinics and in general clinical psychiatric practice. The most important prerequisite for good adherence to long-term medication is having enough time to develop a trustworthy relationship between doctor and patient, independent of the kind of treatment.

11.12 Lithium During Special Circumstances

11.12.1 Lithium Therapy and Anesthesia

Perioperative complications are more common in patients with mental disorders, as their biological response to stress is impaired (Attri et al. 2012). The anesthesiologist must also be aware of potential interactions with anesthetic agents and psychotropic medications before administering anesthetics. Psychiatric medications often given in combination with each other or with other nonpsychiatric drugs generally exert effects on central and peripheral neurotransmitter and ionic mechanisms. As an example, lithium prolongs the neuromuscular blockade, and it can lower anesthetic requirements because it blocks the brainstem release of norepinephrine, epinephrine, and dopamine (Hines and Marschall 2010).

From an anesthesiological point of view, lithium effects entail hazardous risks during surgery, especially when hemodynamic instability occurs, and renal excretion becomes inhibited through interference with sodium and potassium metabolism. Because of this, lithium should generally be discontinued prior to surgery. With an average half-life of 24–36 h, lithium should be discontinued at least 24–48 h before surgery (Huyse et al. 2006). The only justification for not stopping lithium is minor surgery under local anesthesia. When the patient presents normal ranges of potassium, sodium, and creatinine and is hemodynamically stable, able, and allowed to drink during the postoperative period, lithium should be restarted and serum levels controlled within 5–7 days.

11.12.2 Combined Lithium and Electroconvulsive Therapy

Few studies have investigated the effects of the combined use of electroconvulsive therapy (ECT) and lithium. One small controlled experimental study (Thirthalli

et al. 2011) assessed the risks of combining lithium and ECT, with no severe adverse outcomes. A case report published by Sartorius et al. (2005) revealed cases of a prolonged seizure, serotonin syndrome, and focal seizure. Investigators have assumed that preexisting neurological impairments may be responsible for the severe side effects of ECT and lithium when prescribed together. Preexisting electroencephalogram (EEG) abnormalities may be a risk factor for seizure induction as well. Changes in blood-brain barrier (BBB) permeability are also discussed as a confounding parameter on the outcome of combined therapy. The combination of lithium and ECT should be limited to patients presenting a favorable risk/benefit analysis, and physicians still need to be aware of potential but severe central nervous side effects.

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Adverse Effects of Lithium and Their Management

12

12.1 Introduction

Concerns about lithium's adverse effects have been prominent since before the beginning of lithium's use in mood disorders. In fact, lithium's use as a sodium chloride (table salt) substitute in the 1940s and 1950s resulting in clearly documented cases of lithium toxicity played a major role in the resistance to its use after the early reports and studies by Cade and Schou (Johnson 1984). Additionally, adverse effects continue to be a major cause of lithium nonadherence. Lithium's adverse effects can be divided into three groups: (1) side effects, both acute and long term; (2) long-term effects on organ systems; and (3) toxicity.

12.2 Side Effects: Acute and Long Term

Lithium is associated with a number of side effects (see Table 12.1). In short-term treatment, the most common of these are nausea, thirst (with associated polydipsia), polyuria, tremor, and fatigue (Gitlin et al. 1989). Other common side effects are diarrhea, cognitive effects, and weight gain, the latter two achieving greater importance during long-term maintenance treatment.

Nausea tends to be seen early on in lithium treatment and tends to diminish significantly over the first few weeks of treatment (Rybakowski and Suwalska 2006). Lithium ingestion after eating may diminish nausea as may the prescription of

Table 12.1 Side effects associated with lithium

Acute/short term	Long term
Nausea	Cognitive effect
Thirst	Weight gain
Polyuria	Polyuria/thirst
Tremor	Tremor
Fatigue	

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sustained release lithium preparations (see Chap. 11) which enhance more distal absorption, thereby protecting the stomach. Conversely, however, sustained release lithium preparations are inconsistently associated with higher rates of diarrhea. Often, after a period of weeks to months of sustained release lithium, patients may be switched back to lithium capsules without the return of nausea. Dividing the daily dose of lithium may also decrease nausea early on in treatment. Vomiting is rarely seen as a side effect in the absence of toxic lithium levels. Therefore, if a patient on lithium vomits, lithium toxicity (see below) should be considered.

Thirst and excessive urination (polydipsia/polyuria) comprise a common and linked set of side effects which can be seen relatively early on in treatment but continues and even worsens over time in some patients. Up to 70 % of patients experience thirst/increased urination during lithium treatment (Goldberg and Ernst 2012). These side effects are related to the well-documented effects of lithium on renal tubular function (see below for details) leading to nephrogenic diabetes insipidus. Initially, these symptoms are functional and reversible. If lithium is discontinued early on in treatment, these side effects will disappear. Later on, after years of treatment, these changes are less likely to be reversible. For most patients, the polyuria/polydipsia is no more than annoying. As long as thirst mechanisms are intact and water is available, adverse consequences will be avoided. Difficulties arise when water is not freely available (as, for instance, on a backpacking or camping trip in the desert) since patients with lithium-induced polyuria excrete excessively dilute urine, leading to dehydration if sufficient fluids are not ingested.

If the polyuria is more than mildly distressing and/or medication adherence is threatened by the side effect, polyuria/polydipsia may be effectively treated by diuretics. Amiloride, in doses of 5–10 mg daily, may diminish polyuria and associated thirst (Finch et al. 2003). Thiazides, in the form of hydrochlorothiazide 50 mg, also diminish polyuria. Since the latter depletes potassium, potassium levels must be monitored or supplemental potassium administered. Another approach would be the prescription of Dyazide (a combination of hydrochlorothiazide plus triamterene—a potassium-sparing diuretic) which obviates the need for potassium supplementation. Thiazides decrease lithium clearance via increased proximal tubular reabsorption. Therefore, when thiazides are prescribed with lithium, lithium doses should be decreased by approximately 1/3 and lithium levels checked a few days later. Lithium levels should then be monitored more frequently over the next few months to avoid both subtherapeutic levels and toxic levels.

Lithium-induced tremor may be seen at any time during treatment. It is postural and intentional in nature and mimics essential tremor (Back et al. 2014). It is usually but not always symmetric and worsens with activities requiring motor control such as pouring liquids, lifting a glass or cup to the mouth, or writing. (Personal signatures may change substantially due to lithium tremor.) It may be present with nontoxic lithium levels in approximately 25 % of patients (Gelenberg and Jefferson 1995) but virtually always worsens during lithium intoxication. Other etiologies of tremor are additive to lithium-induced tremor. Therefore, anxiety, stimulant (including caffeine) use, the effect of many other medications, and alcohol withdrawal should always be considered as additive factors to lithium tremor. Beta-blockers are

the most established effective treatment for lithium tremors. Propranolol, typically in daily doses of 20–120 mg, is the most commonly prescribed beta-blocker for this purpose, either on a daily basis or as needed. In general, beta-blockers should not be prescribed for those with asthma, congestive heart failure, or significant pathological bradycardia.

Although typically not listed as a common lithium side effect, cognitive impairment is rather distressing to patients (Gitlin et al. 1989). Of course, since bipolar disorder is itself associated with cognitive impairment in a substantial percentage of patients with bipolar disorder (Torres et al. 2007), the etiology of cognitive impairment in a bipolar individual with cognitive impairment must be carefully considered. Other etiologies of cognitive impairment include unrecognized hypothyroidism, substance abuse, the effects of other psychotropic medications such as anticonvulsants and/or antipsychotics, and the loss of hypomanias with the misattribution of euthymic (i.e., normal) cognition. In a meta-analysis, lithium was associated with small but significant impairment in immediate verbal learning and memory and creativity. Other cognitive domains were not significantly affected (Wingo et al. 2009). However, many other patients complain of a more subtle "dullness" and decreased creativity which may be more difficult to measure. Consistent with this, an earlier study found that idiosyncratic associations (a measure of verbal creativity) increased upon lithium discontinuation and decreased again when lithium treatment was resumed (Shaw et al. 1986). No antidote to reverse or ameliorate lithium-induced cognitive impairment is available. Anecdotally, stimulants such as methylphenidate and d-amphetamine or modafinil/armodafinil may be considered in select cases. The dopaminergic stimulants may be associated with hypomania or unwanted stimulant effects. Modafinil/armodafinil seems to not be associated with pharmacological switching into mania (Frye et al. 2007).

Weight gain has been consistently described in association with lithium and is sufficiently distressing for many patients that it is a common cause of treatment nonadherence. As with so many other side effects, other etiologies of weight gain must be considered, such as depression-associated weight gain, the effects of other psychotropic agents frequently prescribed in the treatment of bipolar disorder such as antipsychotics or valproate, the ingestion of high-calorie soft drinks in response to lithium-induced thirst, decreased exercise due to depression, and undiagnosed hypothyroidism due to lithium and, more rarely, edema. The etiology of lithium-induced weight gain is uncertain. Between 25 and 50 % of lithium-treated patients gain significant weight (usually defined as >7 % baseline body weight). Risk factors for lithium-induced weight gain may be higher pre-lithium baseline body weight and higher lithium dose/levels.

Classic strategies for reducing weight gain are universal regardless of etiology: diet and exercise. Other causes of weight gain should of course be addressed, especially limiting the ingestion of high-calorie drinks due to increased thirst and treating hypothyroidism if present. Adjunctive topiramate has been associated with weight loss due to lithium and other mood stabilizers (Chengappa et al. 2006). Metformin has been shown to produce weight loss in patients who have gained weight from antipsychotics (Ehret et al. 2010). It may therefore stimulate weight

loss in lithium-treated patients too. Stimulants may also be beneficial for weight loss, although, as noted above, these should be used very cautiously in bipolar patients due to their other psychotropic properties.

Surprising few studies have examined the effects of lithium on sexuality (Elnazar et al. 2015). In evaluating potential sexual side effects, the confounding effects of depression and the effects of other medications that are known to cause sexual side effects such as antipsychotics and serotonergic antidepressants must always be considered. Additionally, since the rate of sexual side effects in the general population is substantial, simple surveys of lithium-treated patients without comparison groups add little meaningful data. Nonetheless, approximately 1/3 of bipolar patients treated with lithium endorse sexual dysfunction based on established rating scales (Grover et al. 2014). In the only controlled study, aspirin effectively treated lithium-induced sexual dysfunction (Saroukhani et al. 2013).

Dermatological effects of lithium include exacerbation of psoriasis, acne, and hair loss. Treatments are symptomatic and are the same for these symptoms caused by other than lithium. As with other side effects, other etiologies should be considered such as concomitant use of valproate or male pattern baldness for hair loss.

12.3 Long-Term Effects on Organ Systems

The three organ systems that lithium may affect during long-term use are the kidneys, the thyroid gland, and the parathyroid gland (Table 12.2 summarizes these effects).

12.3.1 Lithium and Renal Function

The most important and well known of lithium's organ toxicities is its effect on renal function and structure (Azab et al. 2015). Lithium's effect on renal function was thought to be reversible until the first reports of biopsy proven interstitial nephritis in lithium-treated patients in 1977 (Hestbech et al. 1977). Since that time,

Table 12.2 Lithium's effect on organ systems

Organ	Effects
Renal	Tubular > glomerular
	Long-term effect
	Common thirst, polyuria
	Infrequent renal insufficiency
	Rare end-stage renal disease
Thyroid	W > F
	Associated with antithyroid antibodies
	Easily treated
	Not a reason for lithium discontinuation
Parathyroid	*Probable* increase in hypercalcemia
	Monitor calcium and PTH

increasing data demonstrate that lithium diminishes renal function in a substantial proportion of patients but causes serious renal damage in only a small percentage of those treated.

Lithium accumulates in the collecting tubule in the kidneys, altering renal water excretion via the inhibition of antidiuretic hormone. With ongoing treatment, this initially reversible side effect becomes permanent due to structural changes in the tubular system. Both animal and human renal biopsy studies demonstrate that, with continued use, lithium is associated with a characteristic set of findings: focal nephron atrophy and interstitial fibrosis with relative preservation of glomeruli, characteristic of interstitial nephritis (Gitlin 1999).

Estimating the percentage of lithium-treated individuals with diminished renal function is difficult given the varied definitions of renal insufficiency. Overall, however, lithium treatment is associated with: (1) A diminished capacity to conserve free water as measured by 24 h urine volume or maximal urine osmolality. This deficit correlates with the length of lithium treatment and should therefore be considered progressive, at least over the first many years of treatment. (2) Diminished renal filtering capacity as measured by eGFR (estimated glomerular filtration rate) or creatinine clearance. The decreased eGFR does not consistently correlate with time on lithium and is therefore not necessarily progressive within groups of lithium-treated patients. A small subgroup of lithium-treated patients will demonstrate "creeping creatinine" (Jefferson 1989) with a steady increase in serum creatinine and a steady decrease in creatinine clearance over many years. (3) An even smaller subgroup of lithium-treated patients will progress to end-stage renal disease (ESRD) resulting in dialysis and/or renal transplantation.

The concentrating deficit seen with lithium-treated patients is exceedingly common with rates ranging between 30 and 80 %. As noted above, the thirst and polyuria, symptomatic of the concentrating deficit, are annoying but not dangerous as long as thirst is intact and free water is available. Symptomatic treatment is warranted when the polyuria (especially nocturia) is sufficiently disturbing or significantly interferes with sleep. The gradual increase in serum creatinine known as "creeping creatinine" occurs in 20 % of lithium-treated subjects (Lepkifker et al. 2004). This decrease in renal function is not correlated with the degree of renal concentrating deficits. In another study, in patients in long-term lithium therapy, approximately 1/3 had an eGFR <60 ml/min with 5 % showing eGFR <30 ml/min (Aiff et al. 2015). The degree of renal insufficiency that requires lithium discontinuation is a matter of dispute. As serum creatinine values approach 1.6 mg/dl (140 mmol/L), a renal consultation should be obtained, other potential causes of renal insufficiency should be explored, and a discussion with the patient about other potential approaches to treat bipolar disorder if lithium must be discontinued should be started.

The most controversial question surrounding lithium's effect on renal function concerns the risk of lithium-induced renal failure. Decades ago, it was thought that lithium was never associated with ESRD. Now, however, it is clear that, although unusual, some lithium-treated patients will progress to renal failure in the absence of any other known etiology or contributing factor for renal failure. Biopsy

specimens of these patients are consistent with the findings noted above: interstitial fibrosis, tubular atrophy, and acquired renal cystic disease. In the best population-based study, the relative risk for ESRD in lithium-treated patients was 7.8 compared to the general population, including both those with other risk factors for ESRD and those without (Aiff et al. 2014). However, another large population-based recent study found an increased risk for chronic renal disease but not for ESRD in lithium-treated patients (Kessing et al. 2015a).

The two most important risk factors for ESRD among lithium-treated patients include prior episodes of lithium intoxication (seen in some, but not all patients) and length of time on lithium (average time on lithium in the Aiff et al. (2014) study was 27 years). In one study, lithium-treated patients with serum creatinine <2.5 mg/dl (220 mol/l) were far less likely to progress to ESRD compared to those with creatinine below 2.5 mg/dl (Bendz et al. 2010). Nonetheless, one of us (MG) has treated two patients who discontinued lithium when their serum creatinine values were below 2.5 mg/dl and whose renal function then deteriorated over the next 15–20 years toward incipient ESRD.

There is controversy as to whether the regimen of lithium dosing correlates with differential renal effects (Carter et al. 2013). Earlier animal data suggested that once-daily administration of lithium may result in less polyuria and less renal damage on biopsy specimens compared to multiple dose (twice or three times daily) regimens. This may reflect that having regular time periods with very low lithium levels, as would be seen in once-daily dosing, is renally protective. Although a definitive study is lacking, some, but not all, studies show that once-daily lithium dosing in humans is protective of renal function. No study has shown a positive effect from multiple dose regimens. Since the result of switch studies, in which patients already treated with lithium are changed to a different regimen and are mostly negative, the protective effect of once-daily lithium will likely be seen only in those patients who use this regimen from the beginning of treatment.

Because of these findings, serum creatinine or preferably eGFR should be measured between every 6 months and 1 year during maintenance lithium treatment. Testing urine osmolality or collecting 24 h urine volumes should not be routine since polyuria does not correlate with the risk of progressive renal insufficiency. Additionally, treating polyuria should be based on subjective symptoms, not objective measurements.

Other than ongoing monitoring of renal function, avoiding episodes of lithium toxicity (see below) is the other important recommendation for avoiding renal insufficiency. Discontinuing lithium when renal insufficiency is not advanced (e.g., serum creatinine not greater than 1.6 ng/ml = 140 mmol/L) should be standard. Since discontinuing lithium in this circumstance is not urgent (given the very slow progressive nature of renal changes), the new mood stabilizer should first be introduced and titrated to therapeutic doses before lithium is tapered and discontinued. The optimal time frame of lithium tapering in this circumstance (when another mood stabilizer is already being prescribed at therapeutic doses) is unclear. A reasonable approach would be gradual tapering over 4–8 weeks.

One recent study has suggested an increased risk for renal tumors, both benign and malignant, in patients exposed to long-term lithium treatment who have chronic kidney disease (Zaiden et al. 2014). In contrast, a Danish nationwide, population-based longitudinal study demonstrated that treatment with lithium is not associated with increased rates of renal and upper urinary tract tumors, both malignant and benign (Kessing et al. 2015b). Even though the absolute risk may be rather small (Baldessarini and Tondo 2014), for now, then, this small risk should be balanced against the many potential benefits of lithium.

12.3.2 Lithium and Thyroid Function

Lithium's capacity to decrease thyroid function has been known since the 1960s when the occurrence of goiter in patients receiving lithium was first reported. Rates of hypothyroidism in lithium-treated patients range widely due to the varied definitions of hypothyroidism and the population studied (especially the number of years subjects had been on lithium). Definitions may include overt symptoms of low thyroid states, goiter, low free T4 plus high thyroid-stimulating hormone (TSH), or just high TSH with normal free T4 (usually described as subclinical hypothyroidism). Across studies, prevalence of goiter is 30–55 %; lithium-induced hypothyroidism ranges from 3 to 40 %, averaging 20 % (Lazarus 2009).

Lithium causes hypothyroidism via a number of biological effects. Its primary effect is by inhibiting thyroid hormone release from the thyroid gland. Other possible biological effects are decreasing the conversion of T4 to T3 (which is the more active form of thyroid hormone) and possibly reducing iodine uptake into the thyroid gland. The inhibition of thyroid hormone release results in a higher TSH, the pituitary hormone that stimulates the thyroid gland to make more thyroid hormone with subsequent enlargement of the gland (goiter). If the thyroid cannot compensate despite the increased TSH stimulation, more overt hypothyroidism will result.

Risk factors for hypothyroidism in lithium-treated patients are the same as those seen in non-lithium-treated samples: being female (with a 5:1 ratio in lithium-treated patients), being older, and having antithyroid (TPO) antibodies (which are present in 10 % of lithium-treated patients). It is hypothesized that lithium does not stimulate thyroid antibodies but causes an increase in antibody titers in those who are already antibody positive, whether they are symptomatic or not.

During the course of lithium treatment, TSH should be monitored at least annually. Some experts suggest more frequent monitoring during the first year of treatment. The interpretation of TSH values for patients on lithium is in dispute (Kleiner et al. 1999). Certainly, TSH values >10 mU/l on two consecutive occasions should be interpreted as incipient thyroid gland failure requiring the institution of exogenous thyroid treatment with L-thyroxine, regardless of whether the patient has any symptoms consistent with hypothyroidism. Some experts suggest that TSH values that are higher than the top normal value of the laboratory (4–4.5 mU/L, depending on the laboratory) up to 10 mU/L in patients who are asymptomatic can simply be monitored more closely with TSH measurements every 6 months. Those with

slightly high TSH values (4 or 4.5–10) who show any symptoms consistent with hypothyroidism, such as lethargy, fatigue, or lassitude, should be treated. Lithium-induced hypothyroidism is not a contraindication to lithium. The dose of thyroxine should be sufficient to bring the TSH value into the normal range but not to the hypersuppressed range.

Patients with lithium-induced hypothyroidism who do discontinue lithium usually, but not always, can discontinue their L-thyroxine. In cases of lithium-induced discontinuation in which thyroid replacement therapy continues, it is hypothesized that lithium exacerbated a subclinical hypothyroidism which continued even after lithium discontinuation.

12.3.3 Lithium and Hyperparathyroidism

Lithium's effects on calcium levels and parathyroid function have been appreciated more recently than its effects on renal and thyroid function. A recent meta-analysis showed a 10 % increase in calcium and PTH levels in those treated with lithium (McKnight et al. 2012). Lithium stimulates calcium reabsorption through the renal tubules and directly stimulates parathyroid hormone (PTH) release (Shapiro and David 2015). Calcium and PTH levels may rise at any point in lithium treatment. Few practice guidelines recommend regular monitoring of calcium levels for those on lithium. However, the recent data would suggest that regular calcium monitoring should be considered. Those at higher risk for lithium-induced parathyroidism are women and the elderly. Typical symptoms of hypercalcemia include renal stones, renal dysfunction, osteoporosis, and more nonspecific symptoms such as weakness and fatigue. There is some evidence that lithium-related hypercalcemia may be associated with fewer symptoms compared to those with primary hyperparathyroidism. Whether this reflects lithium's protective effects on bone is unclear.

Treatment options for lithium-associated hypercalcemia/hyperparathyroidism are the same as those for primary hyperparathyroidism. These include surgical parathyroidectomy, continued lithium treatment with monitoring, calcimimetic therapy with cinacalcet, or lithium discontinuation. Given the other treatment options for hypercalcemia and the potential lifesaving effects of lithium, lithium discontinuation may be a greater health risk for some patients than choosing one of the other treatment alternatives. In some cases, the hyperparathyroidism continues after lithium discontinuation.

12.4 Lithium Toxicity

Since before lithium's use in treating mood disorders, its toxicity had been well recognized and described. Lithium has a narrow therapeutic index, i.e., there is only a narrow therapeutic range between inadequate and toxic doses, leading to a greater likelihood of toxicity than for many other medicines (such as SSRI antidepressants or antipsychotics). Lithium toxicity may emerge accidentally in a patient taking

Table 12.3 Signs of lithium toxicity

Mild	Moderate	Severe
Mild, apathy, lethargy	Increased lethargy	Somnolence
Weakness	Confusion, drowsiness	Gross confusion
Unsteady balance	Gross ataxia	Profound loss of balance
Nausea	Vomiting	Urinary incontinence
Decreased concentration	Slurred speech	Random muscle twitching
Worsening hand tremor	Muscle twitching	Coma
Diarrhea		

lithium or due to a conscious overdose as part of a suicide attempt. In the former case, the symptoms emerge more gradually, of course, compared to the latter.

As discussed in Chap. 4, lithium is excreted via the kidneys and is not metabolized by the liver. Therefore, all etiologies of lithium toxicity are due to alterations of salt and water balance and/or renal function. As described in Hansen and Amdisen's classic paper on lithium intoxication (1978), the most common causes of lithium intoxication are dehydration, infectious disease (especially of the GI tract manifesting in vomiting and/or diarrhea), renal disease, new use of diuretics (especially thiazides), or other medications altering lithium renal excretion (such as nonsteroidal anti-inflammatory medications [NSAIDS] and decreased oral sodium intake). Occasionally, a patient will attempt to self-treat polyuria via fluid restriction, resulting in dehydration and lithium intoxication. It must be acknowledged, however, that the etiologies of some episodes of mild lithium toxicity cannot be ascertained. Lithium levels >2.0 mEq/l are always associated with intoxication symptoms. Below this, however, the threshold for nontoxic lithium levels differs markedly across individuals with some patients exhibiting toxicity at levels of 1.0, while others, especially teenagers, are able to tolerate much higher levels. Age is the single most important determinant factor predicting toxic lithium levels. Starting at age 50, older individuals exhibit decreased lithium clearance due to normal age-related renal function changes, requiring lower lithium levels. Additionally, however, older patients may show signs of lithium intoxication at what are usually considered therapeutic levels (Strayhorn and Nash 1977). Whether this is due to medical and neurological comorbidities or the changes in the function of a lithium pump that regulates the ratio of intracellular vs. extracellular lithium is unclear.

Symptoms of lithium toxicity, listed in Table 12.3, range from mild nonspecific symptoms to life-threatening signs and symptoms. Some of the early/mild signs and symptoms—tremor, nausea, and diarrhea—that would likely be seen in accidental lithium overdose may be indistinguishable from the ordinary nondangerous symptoms associated with lithium. However, the emergence of lethargy and ataxia should alert the clinician that the lithium level has increased substantially and should trigger a more thorough evaluation. Additionally, the quality of the lithium tremor changes as the level increases to the toxic range. In lithium toxicity, the tremor—which is the most common symptom, present in almost 50 % of cases—changes from regular to irregular, fine to coarse, and may be more diffuse than in just the

upper extremities. Eating and drinking without marked spilling become close to impossible.

With moderate to severe lithium toxicity, the patient is unmistakably markedly ill. These levels of toxicity constitute a medical emergency. Vomiting (not just nausea) becomes likely, and central nervous system effects—ataxia, confusion, and eventually coma—become dominant features. Renal failure, as manifested by a sudden increase in serum creatinine and an equally sudden decrease in glomerular filtration rate (GFR), is common. With severe toxicity, sinus bradycardia, ST changes, and QT prolongation appear on the electrocardiogram. Treatment of lithium toxicity is discussed in depth in Chap. 11.

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Beyond Lithium: Other Treatments for Bipolar Disorder

13

13.1 Introduction

When lithium was first discovered to be effective, initially for treating acute mania and later for bipolar depression and as a maintenance treatment in bipolar disorder, other therapeutic options were few. First-generation antipsychotics (FGAs), released in the mid-1950s, were unquestionably effective for treating acute mania, but patients often hated their side effects. Additionally, FGAs did not appear to be effective preventive treatments for bipolar disorder. Electroconvulsive therapy (ECT) treated acute mania and acute depression, but both the side effects of this treatment, patients' ambivalence about ECT, and its history of being used in a coercive manner limited its use. Finally, antidepressants, also released in the mid-1950s seemed to help bipolar depression but at the risk of causing a switch into mania.

Now, more than half a century later, the field of pharmacotherapy for bipolar disorder has mushroomed. Beyond lithium, a number of anticonvulsants are mainstays across all three phases of the disorder. Second-generation antipsychotics (SGAs) are popular antimanic medications, supplanting the FGAs. A number of them are also prescribed for acute bipolar depression and as effective maintenance treatments. Finally, polypharmacy—the use of multiple medications to treat bipolar disorder—has become the rule rather than the exception in all phases of bipolar disorder. Although polypharmacy should be avoided whenever possible, the frequency of this prescribing practice indicates that patients and psychiatrists alike are less than satisfied with the effects of monotherapies. From a time when the treatment options were too limited, clinicians now have a remarkable number of choices. This chapter will provide a brief overview of the other treatments aside from lithium that are prescribed for bipolar disorder.

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13.2 Treatment of Acute Mania

Aside from lithium, current first-line treatments for acute mania include both FGAs and SGAs, some—but not all—anticonvulsants, and combinations of two or more of these medications (Cipriani et al. 2011; Yildiz et al. 2011; Grande and Vieta 2015).

13.2.1 Second-Generation Antipsychotics

Although first-generation antipsychotics are also effective, unquestionably, the SGAs now dominate the pharmacotherapy of acute mania. This reflects both their clear efficacy as shown in studies and meta-analyses, their ease of administration, relatively more benign side effect profiles (certainly compared to FGAs), and their rapidity of response compared to lithium. (Aggressive pharmaceutical firm marketing of these agents has certainly added to their popularity.) SGAs with documented efficacy for acute mania include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and asenapine. As with the FGAs, however, it is likely that all agents of this class are effective treatments for acute mania. As with FGAs, dosing schedules for the SGAs in acute mania are similar to those for treating schizophrenia.

In general, SGAs are better tolerated than FGAs. Each agent has a somewhat different profile of side effects with, as an example, some agents being far more sedating (e.g., olanzapine and quetiapine) than others (aripiprazole). Although sedation will decrease manic agitation, effective antimanic agents do not need to sedate. (Lithium is the classic example of a highly effective nonsedating antimanic medication.) Other than prescribing a sedating antipsychotic, an alternative strategy for effectively treating *and* managing acute mania would be the combination of a relatively less sedating antipsychotic plus a benzodiazepine to manage the agitation. As the patient improves, the benzodiazepine can be tapered and withdrawn.

Short-term side effects for the individual SGAs differ in aspects such as sedation, akathisia, weight gain, hyperprolactinemia, and dizziness. Of these, weight gain is the most problematic (and is discussed below).

13.2.2 Anticonvulsants

Two anticonvulsants, valproate and carbamazepine, have documented antimanic efficacy. Other anticonvulsants such as lamotrigine, oxcarbazepine, topiramate, and gabapentin have either shown little antimanic efficacy or have not been evaluated sufficiently.

Carbamazepine was the first anticonvulsant for which systematic studies of its antimanic effects were available. In the United States, one patented form of carbamazepine received an FDA indication for acute mania in 2004. Despite the data demonstrating its antimanic efficacy in placebo-controlled studies and in meta-analyses, carbamazepine is rarely prescribed as a first-line antimanic agent due to its relatively slow time to efficacy, its side effect profile, and its drug-drug interactions.

Additionally, concerns about carbamazepine causing agranulocytosis, rare though it is, with the burden of monitoring blood counts, have made many psychiatrists even less likely to prescribe it. Typical carbamazepine daily doses for acute mania range between 400 and 1600 mg.

The side effects that are most problematic with carbamazepine are dizziness, ataxia, diplopia, fatigue, and nausea. These side effects also make a rapid dose titration, as is necessary in treating acute mania, impossible. Additionally, carbamazepine is a potent enzyme inducer, lowering the blood levels of many other medications that may be co-prescribed and making dose monitoring of other medications more difficult.

Valproate, in contrast, continues to be prescribed with regularity to treat acute mania. In placebo-controlled studies and in controlled studies using lithium as an active comparator, valproate shows clear antimanic efficacy with time to onset similar to lithium. In the best head-to-head study, valproate showed equal efficacy but lower dropout rates compared to lithium (Bowden et al. 1994). In contrast to carbamazepine, valproate's dose can be titrated rapidly to achieve a quicker therapeutic response. Typical daily doses range between 500 and 3000 mg. Some clinicians use a loading strategy for valproate, prescribing 20 mg/kg/day in divided doses and obtaining a valproate level two days later. More commonly, a rapid dose titration, usually starting at 750 mg daily in divided doses, increasing to 1500 mg daily within a few days, is used. Serum valproate level >94 mcg/ml correlates with greater antimanic efficacy, while valproate levels >125 are associated with greater side effect burden (Allen et al. 2006).

Common short-term side effects with valproate are nausea, vomiting, diarrhea, sedation (which may be therapeutic in treating acute mania), and tremor. Mild hepatotoxicity and thrombocytopenia may also be seen.

13.2.3 Benzodiazepines

Benzodiazepines, especially lorazepam and clonazepam, are frequently prescribed when treating acute mania. It is likely, however, that their therapeutic effect is mediated almost exclusively by sedation, in contrast to the "true" antimanic effect of lithium, antipsychotics, and anticonvulsants. Thus, the optimal role of benzodiazepines would be adjunctively to calm manic agitation until another agent becomes effective.

13.2.4 Combination Treatments

Frequently, acute mania is treated by a combination of agents. The most well documented of these approaches is the combination of lithium or valproate plus an SGA. Meta-analyses have demonstrated the additive efficacy of the combination compared to lithium or valproate alone (Scherk et al. 2007; Ogawa et al. 2014). Whether lithium or valproate consistently augments the antimanic

efficacy of SGAs has been evaluated in fewer studies. Benzodiazepines are often combined with antimanic agents for calming purposes. Although never formally tested, lithium plus valproate would also be a reasonable combination to treat acute mania. Of course, combination treatments enhance the side effect burden for the patient.

13.3 Treating Hypomania

Although virtually unstudied, the principles of treating hypomania mimic those for treating mania with the differences of less aggressive dose titrations, possibly lower doses, and less use of combination treatments. Since, by definition, hypomania is both less severe than mania and is always treated in an outpatient setting, treatment adherence and side effects are more central issues than in treating hospitalized mania. Thus, antipsychotics, usually prescribed in lower doses, lithium or valproate, are all reasonable treatments for hypomania. Patient acceptance is crucial to successful treatment of hypomania. Therefore, a discussion of the various options and patient input can be very useful in this situation.

13.4 Treatment-Resistant Mania

For those manias that have not responded to usual treatment, including at least two antipsychotics and at least one combination treatment, three options should be considered. First, although it is rarely used in clinical settings, tamoxifen has been shown to be effective both as monotherapy and in combination (Yildiz et al. 2008; Armollahi et al. 2011). Clozapine seems as effective in treating treatment-resistant bipolar disorder as it is for schizophrenia despite a relative lack of data. Finally, although rarely used, ECT is equally effective in treating mania as it is for depression (Mukherjee et al. 1994). Patient resistance to ECT is a major barrier to its greater use.

13.5 Other Treatments for Bipolar Depression

For many years, research on optimal treatment of bipolar depression lagged far beyond that of acute mania and maintenance treatment. Over the last 20 years, however, an increasing number of studies evaluating many different agents have begun to rectify this gap in our knowledge base. Still, the relative paucity of studies combined with the disparate results in these studies compounded by the controversy over the relative safety and efficacy of antidepressants in treating bipolar depression has left clinicians with a conundrum in creating a coherent treatment algorithm. Table 13.1 shows the major treatment options other than lithium for bipolar depression.

Table 13.1 Treatment options for acute bipolar depression

Medication name generic (trade)	Starting dose	Usual dose range	Efficacy rating	Safety/tolerability	Comments
Quetiapine (Seroquel)	50–100 mg	200–600 mg	+++	Sedation, weight gain	Side effect profile limits strong efficacy
Lamotrigine (Lamictal)	25 mg	100–400 mg	+–++	Rare disastrous rash; otherwise, benign	Clinical experience better than published data
Valproate (Depakote, Depakene)	250–500 mg	1000–2000 mg	+–++	Weight gain, sedation	Infrequently prescribed
Olanzapine/fluoxetine (Symbyax)	6–25 mg	6/25–5/50	++	Weight gain, sedation	Rarely prescribed
Olanzapine (Zyprexa)	5 mg	5–15 mg	+–++	Weight gain, sedation	Rarely used
Aripiprazole (Abilify)	2.5–5 mg	5–15 mg	+	Restlessness, sedation	Clinically more popular than study data suggest
Lurasidone (Latuda)	20–40 mg	20–160 mg	++	Nausea, restlessness	Preliminary positive data
Electroconvulsive therapy (ECT)	N/A	6–12 treatments	+++	Cognitive impairment	Most effective, most burdensome
Antidepressants			+	Switching; rates differ across ages	Avoid monotherapy in BPIs

13.5.1 First-Line Treatments for Bipolar Depression: Mood Stabilizers

From a data viewpoint, the most well-validated treatments for bipolar depression (other than lithium) are quetiapine, lurasidone, and the combination of olanzapine plus fluoxetine. All have received US FDA indications for bipolar depression.

Quetiapine's antidepressant qualities have been demonstrated in five separate large-scale, double-blind, placebo-controlled trials (Sanford and Keating 2012). In each study, quetiapine was significantly more effective than placebo, and 300 mg dosing was generally as effective as 600 mg. In one active comparator study, quetiapine was more effective than lithium and placebo. Although mean lithium levels in that study were 0.6 mEq/l, lower than is usually considered optimal, a post hoc analysis found no antidepressant effect in the subgroup with lithium levels >0.8 mEq/l. In another active comparator study, quetiapine was more effective than paroxetine 20 mg and placebo. Here too, the dose of paroxetine was somewhat low; yet, 20 mg of paroxetine is clearly an effective dose in unipolar major depression studies.

Despite the strength of data supporting quetiapine as a bipolar antidepressant, it is prescribed relatively less frequently than might be anticipated. Assuredly, this reflects the uneasiness by both clinicians and patients about the side effect profile of quetiapine (reviewed below).

Lurasidone has been shown to be an effective agent for bipolar depression (Loebel et al. 2014a). Lurasidone doses in this study—20–60 mg was as effective as 80–120 mg—were relatively lower than the full antipsychotic doses. Lurasidone is less associated with both sedation and weight gain compared to quetiapine.

The combination of olanzapine plus fluoxetine was more effective than placebo and more than olanzapine monotherapy in a large double-blind study (Tohen et al. 2003). Partly due to uneasiness about fixed dose ratio combination preparations and partly due to olanzapine's side effect profile, this combination is rarely prescribed in clinical practice.

Despite a rather weak database, lamotrigine is commonly prescribed for bipolar depression. It has never received a governmental indication for bipolar depression because only one of five double-blind studies was positive (Calabrese et al. 2008). However, pooling the results of all five studies, the more severely depressed patients did respond significantly better to lamotrigine compared to placebo with typical daily doses of 200 mg (Geddes et al. 2009). Lamotrigine's benign side effect profile has contributed to its popularity as a bipolar antidepressant, and most clinicians perceive it as effective despite the weak data. Its major drawback for bipolar depression is the obligatory slow dose titration schedule—6 weeks to achieve the target dose of 200 mg—required to minimize the risk of a high-grade rash.

Although infrequently used for this purpose, some data suggest the efficacy of valproate as a bipolar antidepressant. Each of four small, placebo-controlled studies demonstrated greater efficacy for valproate compared to placebo (Bond et al. 2010). Large-scale studies have not been pursued due to patent issues.

Surprisingly, neither aripiprazole nor ziprasidone has shown efficacy for bipolar depression in double-blind studies.

13.5.2 Combination Treatments for Bipolar Depression

Although virtually never studied, many clinicians use medication combinations to treat bipolar depression. Common combinations are adding one mood stabilizer to another—lamotrigine added to lithium and adjunctive quetiapine or lurasidone added to valproate or lithium are examples. In the only two studies in this area, lamotrigine enhanced lithium's efficacy in bipolar depression, and lurasidone was more effective in combination with lithium or valproate than was lithium alone (Van Der Loos et al. 2009; Loebel et al. 2014b).

13.5.3 Antidepressants for Bipolar Depression

No other area in the treatment of bipolar disorder provokes as much heated discussion and disagreement as the proper place of antidepressants in treating bipolar depression. Disparities exist between many—but not all—academic psychiatrists who recommend against the frequent use of antidepressants vs. the community of clinicians who prescribe antidepressants regularly as both monotherapy and adjunctively for bipolar depression (Baldessarini et al. 2007). Even meta-analyses disagree with one finding only weak, nonsignificant efficacy of antidepressants in placebo-controlled studies (Sidor and MacQueen 2011), while the other found significant efficacy (Vazquez et al. 2013). For now, then, the best conclusion would be that the efficacy of antidepressants for bipolar depression is still unproven.

The key concern about the use of antidepressants for bipolar depression is, of course, the worry that they will provoke a switch into mania/hypomania. Here too there is disparity of data and opinion with one recent meta-analysis demonstrating that antidepressants, when combined with mood stabilizers in most cases, are not associated with increased risk for pharmacological switching into mania/hypomania (Sidor and MacQueen 2011), while other studies seem to find that antidepressants can indeed trigger manias/hypomanias (Ghaemi et al. 2008). Beyond the meta-analyses already cited, a thorough and extensive review is available (Pacchiarotti et al. 2013).

13.6 Treatment of Bipolar II Depression

As much as the treatment of bipolar I depression was neglected for decades, bipolar II depression has been even more ignored. Acknowledging the lack of data, most of the principles used to create a thoughtful treatment algorithm for bipolar II depression are the same as they are for bipolar I depression with a few exceptions: (1) Clinically, lamotrigine is prescribed more frequently for bipolar II depression since the need for robust protection against manic episodes is less necessary in these patients. (2) The balance of risks vs. benefits differs between bipolar I and bipolar II depression in prescribing antidepressants since in the latter, the switch rates are lower and, even when switching occurs, 95 % of the switches are into hypomania, not mania. Additionally, a number of recent studies suggest that at least *some*

bipolar II patients can be safely treated with antidepressant monotherapy (at least when SSRIs are prescribed) (Amsterdam and Shults 2010; Altshuler et al. in review).

13.7 Other Treatments for Bipolar Depression

Two other treatments for bipolar depression are worthy of discussion: modafinil and armodafinil and ECT. Modafinil and armodafinil are nondopaminergic stimulants that have been evaluated as adjunctive treatments for bipolar depression. Although efficacy data show mixed results, switch rates when these medications were added to mood stabilizers were no different than placebo, indicating relative safety for these agents in enhancing mood and energy (Frye et al. 2015). Dopaminergic stimulants, such as methylphenidate and d-amphetamine, are usually prescribed with more caution given their abuse potential and concern about their ability to cause switching (Corp et al. 2014). However, these safety concerns may be excessive and some patients can be treated with these agents safely.

As with its use in severe unipolar depression, ECT is a vital treatment alternative for severe or treatment-resistant bipolar depression (Daly et al. 2001). Its use is limited by its expense; its inherent disruptiveness, three times weekly treatments with anesthesia whether the patient is hospitalized or not; its side effects, especially transient cognitive impairment; and its dreadful image from the past, when it was regulated and used quite differently than it is today. A problem with ECT in bipolar depression is the interaction between ECT and many medications used to treat bipolar disorder. As an example, anticonvulsants interfere with ECT efficacy since they prevent seizures which are a necessary component of ECT efficacy and are typically stopped prior to ECT. Lithium treatment during ECT is problematic and may result in more cognitive impairment that is seen with ECT alone. Some bipolar depressed patients treated with ECT will switch into mania/hypomania. Continued ECT effectively treats this treatment-emergent mania, since ECT is as effective for mania as it is for depression.

13.8 Other Maintenance Treatments for Bipolar Disorder

For decades, the unique nature of lithium as an effective maintenance treatment in bipolar disorder was demonstrated by the fact that, after lithium, the second medication to be indicated for this purpose by the US FDA was lamotrigine in 2003. Since then, however, five SGAs have received FDA indications, yielding a total of seven validated maintenance treatments. Of note, however, each maintenance treatment may have a different profile with differential efficacy in preventing manias vs. depressions.

13.8.1 Lamotrigine

Lamotrigine is a very commonly prescribed maintenance treatment due to its greater efficacy in preventing depressions vs. manias and its relatively benign side effect

profile. Its efficacy was demonstrated in two double-blind studies using lithium and placebo as comparators. In a pooled analysis (Goodwin et al. 2004), lamotrigine was equivalent overall to placebo in the prevention of all mood episodes and was somewhat better at preventing depressions, while lithium was significantly better in preventing manias. Nonetheless, lamotrigine weakly prevented manias compared to placebo. Another non-placebo-controlled study confirmed the findings of equivalent efficacy to lithium in preventing all mood episodes with greater efficacy in preventing depressions and less in preventing manias (Licht et al. 2010). In another study, lamotrigine was also somewhat effective in bipolar II rapid cycling but not in bipolar I rapid cyclers (Calabrese et al. 2000).

Because of its robust efficacy in preventing depression, lamotrigine's role as a first-line drug (and frequently prior to lithium) is in the treatment of depression-predominant bipolar patients. Most bipolar II patients fit this category since their hypomanias (by definition) are not too intense, and their course is dominated by the frequency, prolonged nature, and severity of their depressions. Lamotrigine's major liability is its capacity to rarely (one in many thousands (Mockenhaupt et al. 2005)) cause a potentially disastrous immunological rash called Stevens-Johnson syndrome or, when even more severe, toxic epidermal necrolysis. Because there is some evidence that the risk of these life-threatening rashes correlates with the rapidity of dose titration in the beginning of treatment, lamotrigine has an obligatory slow dose titration, which should not be problematic for a maintenance treatment. Of note, combining lamotrigine with other anticonvulsants, carbamazepine and valproate, carries an increased risk for toxic epidermal necrolysis. Otherwise, lamotrigine has a benign side effect profile, with mild insomnia and occasional nausea but with an absence of weight gain or sedation.

13.8.2 Valproate

Despite its lack of a US FDA indication as a maintenance treatment for bipolar disorder, valproate continues to be prescribed as such, as evidenced by its recommendation in a number of practice guidelines due to a number of features: (1) its clear efficacy in acute mania, (2) its equivalent efficacy to lithium in rapid cyclers (Calabrese et al. 2005), (3) concerns about the methodological features of the largest placebo-controlled trial in which it failed to demonstrate preventive efficacy (Bowden et al. 2000), and (4) general clinical experience. In the only other random assignment study, valproate was generally less effective than lithium as a maintenance treatment in bipolar disorder (Geddes et al. 2010). However, recently, the European authority EMA has withdrawn valproate's indication as a maintenance treatment. Valproate's most common side effects during maintenance treatment are mostly similar to those noted in the section above on acute mania. Valproate side effects that are most problematic during long-term treatment are sedation, weight gain (which is greater than that of lithium), and alopecia which is especially distressing for women. More than other anticonvulsants or lithium, valproate also causes polycystic ovarian (PCO) disease which makes its use problematic in young women (Joffe et al. 2006).

13.8.3 Second-Generation Antipsychotics

Among the most surprising developments in the pharmacotherapy of bipolar disorder has been the consistent evidence of the efficacy of SGAs as maintenance treatments. SGAs have been evaluated both as monotherapies and as combination treatments with lithium or valproate, testing their ability to enhance efficacy beyond that of the other mood stabilizer. Although not all SGAs have been evaluated as maintenance treatments, the consistency of response across at least five different agents suggests a class effect. All SGAs tested seem to show efficacy in preventing manias. However, prevention of depression by SGAs is far less clear and/or consistent. Among the SGAs, only quetiapine has consistently demonstrated efficacy in preventing bipolar depressive episodes (Weisler et al. 2011; Vieta et al. 2008; Suppes et al. 2009). Table 13.2 summarizes the US FDA indication for SGAs. For risperidone, for patent reasons, risperidone long-acting injection (RLAI) has been the only preparation evaluated as a maintenance treatment. There is no reason to think that the efficacy results would not apply to oral risperidone.

As noted in the section on acute mania, the side effect profiles of the different SGAs share some similarities and some differences. The core similarity is that, with the D2 blocking properties of all agents in this class, with long-term use, all SGAs (with the possible exception of clozapine, discussed below) confer a risk for tardive dyskinesia (TD), probably at equivalent rates. The rate of tardive dyskinesia is significantly lower with SGAs than with FGAs, probably at 1/7 the rate (Correll et al. 2004). Even though the absolute risk is rather low—1-year TD prevalence data is <1 % with SGAs—given the long-term, lifetime treatment that bipolar disorder requires, TD is always a consideration.

The other important long-term risks of treatment with SGAs are those of weight gain, the emergence of type II diabetes, and the development of metabolic syndrome that correlates with cardiovascular risk (ADA, 2004). The risk for these side effects is not equal across individual agents. It is highest for olanzapine, slightly less for quetiapine, and much less for the other agents. Nonetheless, practice guidelines recommend regular monitoring of weight, blood pressure, fasting glucose, lipid profiles, and truncal obesity in those treated with SGAs. As noted in Chap. 12, for patients who have gained significant weight from SGAs, metformin and topiramate may be associated with weight loss (Ehret et al. 2010; Chengappa et al. 2006).

Table 13.2 Second-generation antipsychotics as maintenance treatments for bipolar disorder

Medication name generic (trade)	Solo agent	Adjunctive agent	Efficacy for preventing mania	Efficacy for preventing depression
Olanzapine (Zyprexa)	x		Yes	Yes, but less than for mania
Aripiprazole (Abilify)	x	X	Yes	No
Quetiapine (Seroquel)		X	Yes	Yes
Ziprasidone (Geodon)		X	Yes	No
Risperidone long-acting injection (RLAI)	x	X	Yes	No

13.8.4 Carbamazepine

Although prescribed much less frequently as a maintenance treatment now compared to 20 years ago, carbamazepine still should be considered as a mood stabilizer. The data in support of its use is weaker than that for lamotrigine and the SGAs. The majority of the studies compared carbamazepine to lithium, finding it somewhat less effective (Greil et al. 1997; Hartong et al. 2003). There is some evidence that bipolar patients with atypical features do better with carbamazepine than with lithium. However, its side effect profile noted above—the neurological side effects, the small risk of agranulocytosis, and its pharmacokinetic interactions with other medications—makes carbamazepine less appealing to doctors and patients alike.

13.8.5 Other Agents

No other anticonvulsant, such as oxcarbazepine, gabapentin, and topiramate, has shown consistent benefit as a maintenance treatment of bipolar disorder, although topiramate seemed to be effective in long-term noncontrolled studies (McIntyre et al. 2005).

Clozapine has been rarely studied as a maintenance treatment for bipolar disorder. Nonetheless, it is widely considered an important option for treatment-resistant patients for bipolar disorder as it is for schizophrenia (Nielsen et al. 2012). Clozapine's side effect burden—sedation, weight gain, cardiomyopathy, pancreatitis, as well as the significant risk for agranulocytosis with the obligatory blood count monitoring—makes it suitable only for truly treatment-resistant cases.

High-dose (supraphysiologic) levothyroxine (L-T4) has shown efficacy in a few small studies (Bauer and Whybrow 1990; Bauer et al. 2002). Because of the risks of atrial fibrillation and osteoporosis, especially in postmenopausal women, high-dose L-T4 should be considered only for nongeriatric otherwise healthy patients with difficult-to-treat (refractory) bipolar disorder.

13.8.6 Medication Combinations

Combination treatment during the maintenance phase of bipolar disorder is the rule rather than the exception. Many studies have demonstrated the frequency of polypharmacy among these patients. As one example, one naturalistic study found that the average bipolar patient was taking three medications (Post et al. 2010). Although at times this may appear chaotic and sloppy, it reflects the clearly documented finding that, even though many medications prevent bipolar episodes better than placebo, relapse rates among treated patients are still unacceptably high. No specific combination can be uniquely recommended. A well-studied combination is that of lithium or valproate plus an SGA. Lithium plus valproate was more effective than either agent alone in a large random assignment but nonblinded study (Geddes et al. 2010). Although not studied, a common combination is lithium plus

lamotrigine since one of these agents—lithium—is more effective in preventing manias, while the other agent, lamotrigine, is superior in preventing depressions. Many bipolar patients are treated with three or more mood stabilizers—especially rapid-cycling patients who are notoriously unresponsive to all monotherapies—despite any study even examining this approach. Surely, this reflects the desperation of psychiatrists and patients alike, in an attempt to prevent the destructive episodes of bipolar disorder.

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