Lithium specificity in bipolar illness: a classic agent for the classic disorder

We cannot seek or attain health, wealth, learning, justice or kindness in general. Action is always specific, concrete, individualized, unique.

John Dewey (1859-1952)

Therapeutic specificity, or a lack of it by design, is a desirable characteristic for any medication. For instance, in the treatment of bacterial infections antibiotics are often tailored to kill specific bugs or have a broad-spectrum action on a number of pathogens. In most cases, specificity of antibiotic action is clearly advantageous and often essential for an effective cure. Similarly, in treating cancers, chemotherapeutic agents are constantly being refined to target only cancerous cells so as to achieve selective inhibition of growth. Such pharmacotherapeutic selectivity affords greater tolerability and ultimately increases the likelihood of treatment success. In both these fields of medicine a better understanding of the pathophysiology of the disease has led to the development of drugs with greater specificity. In psychiatry, the aim has been much the same, but in comparison, progress has been relatively slow.
In this paper, we briefly examine the meaning and relevance of specificity in the treatment of bipolar disorder, with a particular focus on the use of lithium and its implications for future research.

Specifying specificity

Specificity itself has a number of meanings, depending upon the context within which it is used and how specific one chooses to be. Pharmacologically, specificity is described as ‘the selective attachment or influence of one substance on another’ but more generally, it is used to denote ‘the quality or condition of being specific’. In this paper, we use the latter sense to define and delineate the unique clinical profile of lithium and its pharmacological actions.

Diagnostic specificity of bipolar disorder

In order to meaningfully interpret the findings of clinical trials and pharmacological research investigations, it is essential to have diagnostic consensus with regard to the illness being treated. With respect to bipolar disorder, this has yet to be satisfactorily achieved. The variable diagnosis of manic-depressive illness, its transmogrification into bipolar disorder, and its partitioning into subtypes, with subsequent diffusion into a spectrum of mood disorders, have meant that distinct groups of researchers at different times have attempted to define bipolar disorder using a variety of descriptors, thus limiting comparison of their findings (1–4).

Essentially, there have been two broad approaches to describing mood disorders: dimensional and categorical. Historically, the dimensional or spectrum concept of mood disorders can be traced to Kraepelin’s (5) unitary view of ‘manic-depressive insanity’, in which mania, hypomania, depression, mixed states, and mood temperaments are all regarded as variants of (the same) manic-depressive illness. Manic-depressive insanity, in Kraepelin’s eyes, comprised three domains, namely, mood, thinking, and activity, with excitement or inhibition of these domains in the same or contrasting directions resulting in mania, depression, or mixed states (6).

Throughout the 20th century, Kraepelin’s unitary concept has been successively displaced by a categorical approach and eventuated in today’s major diagnostic classification systems, namely, the DSM and ICD. Both of these systems on the basis of polarity, partition mood disorders into two major classes, bipolar and depressive, and each of these is further subdivided into specific disorders. Within bipolar disorder, subtypes I and II are ‘differentiated’ by the presence of either manic (bipolar I) or hypomanic episodes (bipolar II). However, there is considerable doubt as to whether these disorders are distinct entities or in fact form part of a broader bipolar spectrum that spans extreme psychotic manic states to temperamental dysregulation (4). Support for a categorical nomenclature arose principally from the National Institute of Mental Health Collaborative Depression Study (7–10). This series of studies reported increased familial history concordance, differences in gender distribution (female preponderance in bipolar II but equivalence in bipolar I), and a tendency for diagnostic stability over time within each disorder subtype. In practice, the limitations of this approach soon became apparent, as many clinical presentations cannot be accurately captured by these ‘categories’. Heightening interest in mixed states further obfuscated the boundaries of disorders (11) and led to the positioning of bipolar II disorder along a continuum between the more ‘clearly defined’ polarities of major depressive disorder and bipolar I disorder. Consequently, reconsideration of the spectrum is garnering renewed enthusiasm (3, 12), along with the possibility of multiple bipolar subtypes, bipolar I–IV (1). This spectrum approach is supported by observations of a similar age at onset for both bipolar I and bipolar II disorders, the same core features in mania and hypomania, the frequent occurrence of hypomania in the course of bipolar I disorder, and the gradation of symptoms across the two subtypes, with depressive symptoms typically more severe in bipolar II and manic symptoms more severe in bipolar I (6).

Thus, in an attempt to reconcile these seemingly opposing constructs, it has been posited that the prevailing evidence supports both a spectrum distribution of mood disorders and the presence of archetypal cases. The acknowledgment of this dualism permits the coterminous binate conceptualization of a continuum with superimposed categories that exist at specific points along the spectrum (3, 13, 14).

Adding further complexity to diagnostic dilemmas within bipolar disorder is the controversial expansion to include juvenile bipolar disorder. A number of practice guidelines in bipolar disorder provide recommendations for the management of juvenile bipolar disorder (15–17), but a review has highlighted a lack of consensus amongst these guidelines, particularly regarding the diagnostic and symptomatic presentation of juvenile bipolar disorder (18).

In addition to the difficulties of heterogeneity within bipolar disorder, the phenotype is often indistinguishable from other disorders such as...
major depression and schizophrenia. With respect to the latter, it is interesting to note that the delineation of the diagnostic boundaries of schizophrenia has seemingly moved in the opposite direction relative to manic-depressive disorder, especially in the past three decades. Since the seminal U.S.-U.K. cross-national studies (19), the DSM-III and its successors have defined the schizophrenia phenotype fairly narrowly, whereas the diagnostic boundaries of bipolar disorder have expanded and shifted significantly away from the classic descriptions of manic-depressive disorder. Thus, while the prevalence rate of schizophrenia has barely altered, remaining around 1%, the expansion of what is now termed bipolar disorder has led to a doubling and perhaps tripling of its prevalence rate, with most authorities accepting figures of 3% to 5%.

Not unexpectedly, these definitions of bipolar disorder are extremely pertinent to any discussion of the specificity of lithium, especially as presentations of bipolar disorder are often subsumed within schizoaffective disorder (20), in particular mixed states and mania with psychotic features. Similarly, bipolar depression, the usual calling card of the illness, is routinely treated as unipolar (major) depression, explaining how early treatment studies often included both patient populations. Indeed, such is the overlap of bipolar disorder with other illnesses that it has been suggested that bipolar disorder is better conceptualized within a psychosis cluster, alongside schizophrenia, and separate from the emotional disorders that encompass unipolar depression (21).

In summary, within this milieu of diagnostic uncertainty (22), any evidence of specificity of action that is drawn principally from clinical trials must be considered with caution. This caveat is particularly pertinent to lithium, given that it has been tested in trials and used in clinical practice for over half a century. In fact, in many of these instances lithium has been used in bipolar disorder patients who today would only form a subgroup of that diagnostic entity.

Clinical therapeutic specificity of lithium

A lack of therapeutic specificity has plagued the clinical treatment of psychiatric disorders, and continues to do so. Antidepressants, many of which have been discovered somewhat serendipitously, have been successful in the treatment of major depression, particularly acute moderate-severe depression (23–27). Remarkably, antidepressants are equally effective, if not more so, in treating many anxiety disorders, and therefore it is not unreasonable to speculate that had they initially been used principally in treating anxiety they would perhaps now be called anxiolytics. In practice, antidepressants, in particular tricyclics, are also used for assisting sleep and providing analgesia, further underscoring their putative lack of specificity for depression. However, within the treatment of depression their therapeutic profile does show some specificity, with many antidepressants demonstrating acute efficacy against melancholic symptoms, but much less benefit in long-term maintenance therapy or prophylaxis (23, 24). Further, some degree of phenotypic specificity can perhaps be insinuated from their lack of efficacy in the treatment of bipolar depression (23, 28, 29).

In a similar vein, largely because of a better extrapyramidal side-effect profile, the atypical antipsychotics have negotiated the difficulties of tolerability that constrained the use of the typical antipsychotics, and have gradually assumed additional roles beyond their basic neuroleptic function. For instance, a number of atypicals have been successfully used to augment the action of antidepressants in the treatment of major depression (30), and as a class of agents they are gradually gaining prominence in the management of bipolar disorder. Indeed, their putative efficacy in managing aspects of bipolar disorder such as acute mania, depression, and prophylaxis has prompted speculation as to whether these agents should qualify as mood stabilizers (31, 32). However, in the treatment of bipolar disorder, long-term efficacy and tolerability data for atypical antipsychotics are lacking, and therefore their positioning on par with agents such as lithium is somewhat premature. Traditionally, the term mood stabilizer has been used to describe lithium and valproate, with perhaps only lithium seemingly qualifying for the most stringent of definitions. However, the definition of this term remains contentious and it is of note that formally no agent has ever obtained an indication from the U.S. Food and Drug Administration as a mood stabilizer (33), perhaps lending support to the notion that it has greater commercial salience than scientific utility (31, 32, 34, 35). Ideally, a mood-stabilizing agent should have acute efficacy for both mania and bipolar depression and also possess prophylactic properties that warrant maintenance use. Whether any single agent can in fact achieve this, or indeed whether this is a desirable goal, is not known. However, amongst the currently available agents lithium remains perhaps the best qualified and certainly the most experienced, and examining the cross-sectional and longitudinal efficacy data pertaining to lithium use in the treatment of bipolar disorder serves to demonstrate this.
Lithium in acute mania

Lithium is widely advocated in the treatment of classic acute mania (characterized by euphoria) and the majority of current practice guidelines promote lithium monotherapy as a first-line option for the treatment of mania alongside alternatives such as valproate and atypical antipsychotics. Following early observations (36, 37), preliminary studies demonstrated lithium’s robust superiority over placebo (38–41), even though they were somewhat limited methodologically by crossover designs or nonrandomized group allocation. A recent review of trials over the past 30 years has reaffirmed the primacy of lithium in treating acute mania (42), though in practice a prerequisite of treatment compliance and a noticeable delay in onset of action often constrain its use as compared to other drugs that are more easily administered and have greater response immediacy. However, both clinically and in research, lithium is still regarded as the gold standard comparator against which the effectiveness of other medications should be gauged. In such comparator trials, lithium once again appears to be superior to placebo and demonstrates comparable efficacy to all other medications. However, findings from early studies suggest that lithium does have some limitations with diminished efficacy in patients with agitation (43–45) that is not related to psychotic symptoms per se (46–50), though a combination of lithium or valproate with an antipsychotic appears to be more effective than either as monotherapy (50–52). It is important to note that this apparent effectiveness constraint is largely because of its slow onset of action, and that in terms of efficacy in treating aggression, lithium has been shown to have an effect in a number of clinical trials (53) and was noted to be potentially useful in this regard by Cade himself in his landmark paper (36). Interestingly, a poor response to lithium is also noted in dysphoric or mixed mania, for which valproate and carbamazepine are the preferred agents. However, in the treatment of rapid-cycling bipolar illnesses, lithium remains first line, but only in combination with an antipsychotic or valproate (54–56).

Lithium in acute bipolar depression

The acute antidepressant effect of lithium monotherapy in bipolar depression has not been firmly established (57, 58), despite many open and controlled studies demonstrating a clear antidepressant effect. Clinicians remain reluctant to use lithium as an antidepressant even though it maintains a prominent role in most bipolar disorder treatment guidelines because of expert preference (59). In fact, in practice, lithium is widely regarded as primarily a prophylactic agent with antimanic properties (60).

Early trials in unipolar and bipolar depression clearly alluded to the superiority of lithium over placebo (40, 41, 61–67), but because these studies were generally small and of relatively short duration (some as little as 10 days), their findings were regarded as tentative. These studies were also criticized because of the abrupt cessation of lithium prior to the commencement of the double-blind phase of the trials, and this may well have contributed to an elevated relapse rate in the placebo group (68). However, more recent studies in unipolar depression, the findings from which have been examined through meta-analysis (69), have shown that lithium is effective across a range of serum levels and that it is superior to placebo and perhaps on par with tricyclic antidepressants (70–75). Of note, one of the factors that appears to predict a better outcome in treating depression with lithium is bipolarity (63, 66), with responses in unipolar depression also favouring those with a family history of bipolar disorder (76). In the treatment of bipolar depression, lithium is disadvantaged by a delay in effect of 6–8 weeks, compared to 6–10 days in acute mania (77).

Lithium prophylaxis in bipolar disorder

Lithium is the unanimous first-line choice for the maintenance treatment of bipolar disorder; however, because of illness factors (for example, predominance of depression), tolerability profile, patient preference, and treatment resistance, many patients are prescribed an alternative. Typically this includes valproate, carbamazepine, or lamotrigine, but increasingly, atypical antipsychotics are also being considered as maintenance therapy for bipolar disorder. However, in the absence of long-term (10 years or more) evidence, such prophylactic use seems premature, and in practice most patients appear to relapse on extended atypical antipsychotic treatment and then have to revert to combination strategies that include the reintroduction of an anticonvulsant or lithium. The extrapolation of acute episode treatment strategies into maintenance therapy has rekindled discussion as to whether treatment of an acute bipolar episode should take into consideration the preferred prophylactic treatment or whether the treatment that proves to be successful acutely should be extended to maintenance therapy (54, 78).

Clinically, the successful implementation of maintenance therapy is critical and perhaps more
important than the acute treatment of bipolar episodes. In this regard, lithium is more effective than placebo in preventing all new mood episodes, as reported in a Cochrane review of randomized controlled trials (79), such that for every five patients treated with lithium (for greater than one year), one patient avoids relapse (80). Further, it is noteworthy that the effects of lithium stabilization are usually sustained for many years and that if treatment is briefly interrupted, prophylactic efficacy can often be re-established (81, 82).

Maintenance studies show that lithium is superior to placebo in preventing manic episodes and that in the prevention of depressive relapses there is a trend in its favour (83–87). However, two recent meta-analyses of lithium treatment (88, 89), though corroborating the reduced risk of manic relapse, found only equivocal support for the reduction of risk of depressive episodes.

Additional clinical effects of lithium

Antisuicidal properties of lithium

The lifetime risk of suicide in bipolar disorder is approximately 15 times that in the general population, with up to 20% of untreated patients eventually committing suicide (90, 91). Long-term lithium treatment has been shown to reduce suicidal behaviour and the risk of suicide in both recurrent depression (92) and bipolar disorder (93, 94). Recent reviews of randomized, controlled trials and open studies suggest that long-term lithium treatment in bipolar disorder reduces the risk of suicide by up to 80% (95, 96), and a meta-analysis of lithium treatment in recurrent depression confirms its reduction of suicide risk (97). However, balanced counterpoint to this is the likelihood of diminished treatment adherence given the potential side-effect burden, the increased risk of relapse upon rapid discontinuation (98), and the risk of a possible overdose, because despite its apparent protective properties, lithium itself can be toxic when taken in overdose (99).

Still, lithium truly distinguishes itself as perhaps the only agent to have a substantive antisuicidal effect. The effects of other psychotropics on suicidal behaviour and suicide are equivocal, but of note, the risk of suicide is almost three times greater with valproate as compared to lithium (100), a disadvantage of the anticonvulsant that also extends to carbamazepine (101). This argues strongly for specificity of action, especially when coupled with the finding that bipolar patients off lithium are much more likely to attempt suicide than those taking lithium (102). This preponderance of suicides during off-lithium periods as opposed to when being treated with lithium has been explained by some as a consequence of its effect of preventing depression (103). However, others posit that lithium is unique by virtue of its serotonin agonism and that this underpins its antisuicidal properties (93, 94). This in itself is difficult to prove, or indeed disprove, on the basis of prevailing evidence; however, the specific anti-aggressive properties of lithium that have been demonstrated in both animal and human studies (104) advocate strongly for lithium specificity. The argument in favour of lithium antisuicidal specificity is further strengthened by the findings from studies that have shown the effect to be evident in patients that do not benefit from lithium treatment in terms of episode reduction (105).

Lithium in the treatment of acute unipolar depression, treatment-resistant depression, and recurrent depression

Acute effect of lithium in major depression. As alluded to earlier, lithium has demonstrated efficacy in the treatment of acute unipolar depression (65, 70–75, 106); however, a somewhat modest effect as compared to traditional antidepressants, such as imipramaine, was anticipated by early studies (61). Indeed, some studies of this era failed to show any separation of lithium from placebo (41); however, Souza and Goodwin (69) conducted a meta-analysis of these preliminary studies and confirmed the efficacy of lithium in major depression to be perhaps on par with antidepressants, but certainly better than placebo.

Acceleration and augmentation effects of lithium in the treatment of major depression. In addition to its putative role as an antidepressant, lithium has been studied as an augmentation agent in combination with a whole range of antidepressants. Researchers have also sought to determine whether lithium possesses an acceleration effect; however, the findings in this regard remain equivocal. In comparison, its efficacy as an antidepressant augmentation agent is impressive and has been demonstrated in both unipolar and bipolar depression (77, 107). In fact, in the treatment of major depression, lithium is the most well-established augmentation strategy, and is often considered first line when the response to antidepressants is inadequate. Its efficacy as an augmentation strategy in combination with selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclics has been confirmed in over 12 double-blind, controlled trials and many open-label trials (108, 109). However, its efficacy as an
augmentation agent of antidepressants such as venlafaxine, mirtazapine, or duloxetine has yet to be established (110). Of note, there has been some criticism that earlier trials of lithium augmentation may be confounded by the failure of trials in the 1980s to differentiate between unipolar depressed and bipolar depressed patients (110).

Lithium in the treatment of recurrent depression. Given the demonstrated efficacy of lithium in bipolar disorder prophylaxis, it is interesting to note its putative efficacy in the treatment of recurrent unipolar depression (111, 112). Indeed, a recent Cochrane review (113) concluded that there was ‘adequate efficacy’ for lithium in the prevention of relapse in unipolar affective disorder, but that its relative efficacy compared to antidepressants is not known. Further, empirically it is likely that the effects in unipolar depression are modest as compared to those observed in bipolar disorder; however, again, the extent of any such differential is not known.

Lithium in the treatment of schizoaffective disorder and schizophrenia

In addition to its effects in mood disorders, early studies indicated that lithium benefits patients with schizoaffective disorder (114–118), but that the effect is less than that found in patients with bipolar disorder (119, 120). Subsequently, it became apparent that it is patients with prominent mood symptoms that are more likely to respond, particularly if they have manic symptomatology. This is corroborated indirectly by both early and more recent studies of patients with schizophrenia in which there is no significant response to lithium (121–123). A recent Cochrane review of 20 studies involving 611 patients with schizophrenia (124) that examined both lithium monotherapy and its adjunctive use concluded that lithium monotherapy and its adjunctive use concluded that lithium monotherapy does not appear to be an effective treatment for schizophrenia and that the benefit of augmenting antipsychotics with lithium was inconclusive. Once again, the effects were associated with mood and the response to lithium diminished when patients with schizoaffective disorder were removed from the analysis.

In summary, lithium possesses a specific clinical therapeutic profile across the phases of bipolar disorder, with demonstrated efficacy particularly in prophylaxis. In addition, it has unique antisuicidal properties and is useful as an augmenting agent in the treatment of major depression. These findings underscore the specificity of lithium action in bipolar disorder.

Pharmacological specificity of lithium

Despite the ubiquitous use of lithium and its grandfather status in the armamentarium of bipolar pharmacotherapy, its putative mechanisms of action are just beginning to be understood. Much of the early work on the actions of lithium on the biogenic amines and their receptors was driven more by the prevalent theories of mood disorders than a real attempt to understand lithium itself. Consequently, even though lithium showed effects on various biogenic amines, it is most likely these were ‘downstream’ effects, unlike its more definitive and direct actions on the intracellular second messenger systems (125).

On the contrary, assessment of lithium’s actions at second messenger pathways has not only borne fruit, but has even spawned unexpected results. For instance, substantive in vitro evidence suggests that at therapeutic concentrations, lithium inhibits inositol monophosphatase (IMPSa) (126), and consequently manages to compromise phosphatidyl inositol signaling that is coupled to dysfunctional G-protein processes in the brain. This specific targeted interaction is thought to underpin its ability to quell the symptoms of bipolar mania. However, though this is an attractive postulate, it has not been possible to test as yet because of a lack of suitable in vivo IMPase inhibitors for use in humans.

On the other hand, a novel class of drugs for bipolar mania has emerged largely as a consequence of tests that were conducted on the inhibitory effects of lithium on protein kinase C (PKC) enzymes (127). Tamoxifen, a drug used in human breast cancer and a PKC inhibitor, has shown efficacy in two independent, single-center, monotherapy studies for bipolar mania (128, 129).

Another unexpected corollary of evaluating the molecular targets of lithium action is the discovery of its inhibition of glycogen synthetase kinase (GSK) enzymes. This occurs at the therapeutic concentrations used in bipolar disorder. Further, GSK inhibitors have shown antidepressant properties, and GSK itself appears to be involved in synaptic plasticity, circadian rhythms, and gene transcription, all of which are implicated in bipolar disorder (130). Naturally, as GSK inhibitors are developed for use in humans, it is likely that some of them will be tested in bipolar disorder.

Interestingly, a few of the anticonvulsants used in bipolar disorder appear to share some, but not all, of lithium’s actions at molecular targets (127), and it is possible that antipsychotic drugs also affect similar intracellular targets. However, based on present findings, antipsychotic drugs appear to
have a more direct effect on first messengers, and are generally broad and nonspecific in their effect on downstream targets, in comparison to lithium.

In summary, lithium appears to have a unique pharmacological profile that holds significant potential with regard to understanding bipolar disorder and the development of novel therapeutic agents.

Discussion

In this brief paper, the argument for lithium specificity has been put forward on the basis of data from treatment trials and clinical practice. The latter is especially important in the case of lithium, where there is an overwhelming wealth of real-world experience, and this is perhaps why it remains positioned prominently in most contemporary treatment guidelines for the management of bipolar disorder. Clearly, until we are better informed as to the precise mechanism of action of lithium and are able to better test its properties, its purported specificity of action remains essentially an assertion. However, the evidence for this argument is persuasive, and when considered in comparison to other agents, lithium does appear to have some unique qualities such as its antisuicidal effect.

In clinical practice, lithium’s use has been gradually diluted over the past six decades by the introduction of additional agents and the concurrent broadening of the concept of bipolar disorder. Its apparent decline in efficacy is largely a consequence of poor a priori identification of patients that are most likely to respond. The latter group, referred to as ‘lithium responders’, remains prevalent, with perhaps as many as one third of patients with bipolar disorder falling into this ‘category’ (131). Therefore, in practice it is important that lithium responders are actively sought and treated appropriately (see Table 1 and Fig. 1) (131, 132). Accurate detection and assessment of these cases are essential so that the profile of lithium response can be better understood and further refined through future research.

Conclusion

Lithium is a completely unique psychotherapeutic agent, as can be confirmed after 60 years of clinical use and intense study. It was introduced at a time when the only pharmacological treatments for most psychiatric conditions, especially mania, were sedative agents. We must note the historical impact that in 1949 lithium was reported to calm manic patients and in fact ameliorate the psychopathological manifestations of mania without sedation or any significant cognitive impairment. Its clinical value has been maintained over the 60-year period since and its clinical profile has been enlarged as aspects of its mode of action have been illuminated. The accumulating data have strongly tended to support a claim for its specificity in psychiatric usage. All that remains, therefore, is for us to better understand its unique profile and apply it more specifically to those who are most likely to benefit, namely, patients with ‘classic’ bipolar disorder.

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