

Hypothesis Paper

Mood-stabilizers: the archeology of the concept

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Objective: To review the history of ‘mood-stabilizing’ treatments.

Method: We have reviewed primary source data on the origin of the use of current mood-stabilizers.

Results: This historical record on the origins of the mood-stabilizers points to a more ambiguous picture as regards pharmacotherapeutic specificity to bipolar disorders than is commonly conceded.

Conclusions: This review suggests a need for alternative formulations of the concept of a mood-stabilizer. An alternative to the currently dominant paradigm is that these agents have treatment effects, which need to be matched more precisely with patients’ constitutional types in order to optimize outcomes.

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In recent years the treatment of bipolar mood disorders has changed dramatically with sodium valproate, carbamazepine, lamotrigine, and other anticonvulsants now used regularly in addition to or *in lieu* of lithium. There is a general acknowledgement that pharmaceutical company interest in the area of bipolar disorders has played some part in sustaining a wider interest. But this wider interest has also led to the emergence of conceptual models challenging traditional notions in this therapeutic domain. For example antidepressants are routinely used in the depressed phase of a bipolar disorder, but there is in fact very little evidence to support this practice (1) and some reason to believe that antidepressants paradoxically may make the problem worse (2, 3). There are clear implications of such perspectives for the theoretical models that underpin clinical practice.

A great deal hinges on the concept of a mood-stabilizer. For three decades, lithium stood as what would now be called a mood-stabilizer in contrast to the ‘antidepressants’. The answer to the question what is a mood-stabilizer was simple – it was lithium. The emergence of other compounds forces us to go further. What does it now take to show a

drug is a mood-stabilizer? Will defining a drug as a mood-stabilizer then lead to people who respond to that drug being diagnosed as bipolar patients? Would this be appropriate?

This paper attempts to shed light on these questions by charting aspects of the development of anticonvulsants for mood disorders. An accompanying paper will provide comparative data on the incidence and prevalence of service utilization for patients diagnosed as having bipolar mood disorders and other data such as inter-illness intervals from the pre- and postlithium periods.

The archeology of mood-stabilization

The initial use of lithium for mania created an impression that the manic pole of manic-depressive illness might almost involve a lithium deficiency state. The possibility of what would now be termed mood-stabilizing effects arose in the late 1960s. Two studies by Schou and Baastrup laid the basis for claims that lithium was prophylactic for manic-depressive episodes (4–6). But the response to these claims was vigorous with critics of the concept arguing that the results of the naturalistic studies

that formed the basis for claims for lithium's prophylactic effects might simply reflect a regression to the mean, or the effects of a withdrawal syndrome. A 'mirror-image' service utilization study of patients before and after lithium by Angst, Weiss, Grof, Baastrup and Schou in 1970 (7), and a randomized controlled trial (8) appeared to settle the issue – lithium was what would now be termed a mood-stabilizer.

However, the data on service utilization from the study by Angst et al., which did so much to lay the basis for the concept of a mood-stabilizer in the 1970s, from the perspective of the present look less clear-cut than standard interpretations of the study suggest. In part, this is because by 1970, the 'mood-stabilizing' properties of valpromide had already been discovered, and reports were just about to emerge of lithium's benefits in conditions other than manic-depressive illness.

The origins of valproate/valpromide

The origins of valproate and valpromide lie in the Second World War and efforts by German scientists to produce butter substitutes (9). These efforts led to the synthesis of valproic acid. After the war valproic acid was used as a common diluent for other drugs. In 1963 George Carraz of the Laboratoire Berthier at Grenoble, when asked to test out a new product for possible anticonvulsant properties dissolved the new compound in valproic acid. Testing failed to show any correlation between different doses of the experimental compound and anticonvulsant activity but yet the mixture was anticonvulsant. Carraz realized that the anticonvulsant properties stemmed from valproic acid and titrating the dose of this demonstrated the issue conclusively.

Carraz synthesized valproate (Depakine) and valpromide (Depamide) derivatives of valproic acid. The conventional wisdom of the time had it that an azote moiety would enhance the psychotropic properties of a compound, and it was this that led to the synthesis of valpromide. Valpromide in fact protects animals from epileptic convulsions triggered by strychnine where valproate does not. Valpromide also crosses the blood brain barrier more readily leading to higher CNS concentrations than valproate.

Carraz had a link with Sergio Borselli a psychiatric trainee with Pierre Lambert at Bassens Hospital in Rhône-Alpe. This led to the primary tests of the anticonvulsant properties of both valproate and valpromide in Bassens Hospital (10–12).

At that point in time most large asylums in Europe had significant populations of epileptic

patients – from 10 to 20%. This gave a ready population in which to try out a new anticonvulsant. Borselli and Lambert initially found valpromide intensely sedative, particularly when added to other anticonvulsants such as phenobarbitone. When valpromide was finally administered on its own, it became clear that it had psychotropic in addition to neurotropic effects. This has been described by Lambert as follows 'patients felt more themselves, the mental stickiness, viscosity that had sometimes been there on older agents, was less. We saw the disappearance of tendencies to depression, sometimes even a mild euphoria' (13).

Epilepsy was then thought to predispose to both schizophreniform developments, and an epileptic personality disorder. Epileptic patients were seen as importunate, manipulative and viscous in their personalities. These patients were frequently detained in hospital not because of their convulsions but because of the social disturbances they caused. They were thought to have impulse control disorders, which underlay their inability to adapt to normal social life. The other feature of their personalities was a certain obsessionality. On valpromide, these social disturbances and the characteristic importunate behavior of hospitalized epileptics appeared to change. Female patients in particular were less likely to end up in conflicts, less likely to provoke others in their surroundings, and less likely to self-harm. This led Lambert and Borselli to ask whether valpromide reduced self-harm tendencies; was it anti-masochistic?

These issues return in the case of the discovery of carbamazepine and pose a real question. The degree of control of convulsions is not significantly better now compared with before but it is clear that epileptic patients do not end up in mental hospitals in a way that they did before. Is this because of a beneficial effect of these drugs on personality and general integration that has been all but un-investigated? Is this beneficial effect what underpins mood-stabilization?

At this time, lithium was unavailable in France or was more generally thought of as being ineffective. There was a premium therefore on finding effective treatments for manic-depressive disorder. The standard maintenance regimes at the time involved the use of antipsychotics such as chlorpromazine or levomepromazine. The sedative properties of valpromide led to its use in combination with chlorpromazine for agitated and manic patients, just as phenobarbitone had been used. On recovery, patients left on valpromide alone showed an enhanced compliance compared with patients on chlorpromazine. Altogether Lambert et al. studied the drug in approximately 250 patients

and concluded that valpromide had distinct psychotropic effects that were of benefit in the treatment of both acute manic states and in the maintenance treatment of manic depressive illness (14). This led to a study looking more closely at 32 patients and at the impact of valpromide on rates of hospitalization before and after exposure to this agent. In line with the earlier findings of Angst et al. for lithium, there appeared on valpromide to be a fall in the number of manic episodes by 50% and a decrease of 60% in the duration of hospitalization (15).

Valpromide at this stage, however, was not promoted by Laboratoire Berthier as valproate was selling well as an anticonvulsant both in France and abroad. Valproate also began to be used for mood disorders and in 1980 Emrich et al. (16) reported on its usefulness for the management of mania without knowing about the prior use of valpromide.

The origins of carbamazepine

In the early 1970s lithium was not available in Japan. This led to the use of a wider variety of agents to manage manic-depressive disorders than were being used in countries where lithium was available. Japanese hospitals were also in the process of institutionalizing with a large increase in the hospital population following the discovery of chlorpromazine in contrast to the reductions elsewhere (17). Japanese psychiatry was neuropsychiatrically oriented and the treatment of epilepsy lay within the domain of psychiatrists. This meant that a considerable number of patients were treated in asylums for epileptic or related conditions. As a result, carbamazepine, a tricyclic agent, came into use within the asylum following its release as an anticonvulsant during the 1960s.

The availability of and sedative properties of carbamazepine almost inevitably led to its use *in lieu* of other sedative agents such as the barbiturates in manic patients. In an echo of the valpromide story, it was noted that the use of carbamazepine contributed something distinctive to the management of both epileptic and manic patients (18, 19).

These factors laid the basis for a clinical trial of carbamazepine in the treatment of manic-depressive illness (20–22). When written up in English, this trial in which carbamazepine was compared with chlorpromazine demonstrated comparable results to chlorpromazine (23). However the article had a poor reception in the Western literature with the criticism that almost homeopathic doses of chlorpromazine had been used (250 mg/day) and

that therefore there was no evidence of efficacy for carbamazepine (19). This was during a period when megadose regimes of neuroleptic agents were used in the West against which a 250 mg dose of chlorpromazine may well have looked indistinguishable to placebo as a comparator. The protocol used however was exactly the same protocol used to investigate lithium and these results were not contested. The results of carbamazepine and lithium indeed appeared to be comparable (24, 25).

Carbamazepine however did not emerge into wider use in the West until its psychotropic effects were documented by Ballenger and Post in 1980. By the time it emerged into wider use, it was clear that carbamazepine had interesting psychotropic properties. It had been used in Japan for a wide range of conditions and it was noted to be useful in stabilizing aggressive outbursts in young men. Young men with impulse control disorders reported that a break was interposed between them and their impulses so that they were allowed a pause for reflection that they did not have before. This use of carbamazepine entered into the Western literature as a use in the management of episodic dyscontrol syndrome (19, 26).

Parallel developments

Lithium was undergoing a parallel evolution. When first introduced in the 1950s, it had appeared to be a specific treatment for manic-depressive illness. From there, it migrated during the 1960s to become a prophylactic treatment. In the early 1970s, a study by Sheard in prisoners demonstrated an anti-irritability, or anti-impulsive action that led to a reduction in violent behavior among prison inmates (27). This study, which was immediately replicated (28), questioned the basis for the supposed specificity of lithium's effects to manic-depressive illness. Paradoxically at the same time the concept of bipolar disorder was broadening out to encompass anyone who might respond to a mood stabilizer. The licensing of lithium in the United States in conjunction with other historical processes was leading to a re-diagnosis to manic-depressive illness of many patients formerly diagnosed as having schizophrenia (29, 30).

But there is another neglected history here. Through the 1960s a variety of other anticonvulsants were also used for non-epileptic indications. These included diphenylhydantoin (31, 32), beclamide (33) and sulthiame (34, 35). These drugs were used a variety of psychotic and behavioral conditions including what were later called conduct disorders in children and are now liable to be diagnosed as juvenile onset bipolar disorders. This

use of drugs like sulthiame and diphenylhydantoin, however, unlike the use of carbamazepine and valproate did not get linked to bipolar disorders at the time and did not lead to the concept of mood-stabilization.

The emergence of mood-stabilization

Based on reports of the effectiveness of carbamazepine for mood disorders, Post et al. (36–38) suggested that the efficacy of this tricyclic anticonvulsant might be explained if episodes of mood disorder were conceptualized as convulsive equivalents. Mood stabilization might then involve a reduction of the kindling effects that primed subsequent episodes. While Schou almost 20 years earlier had talked about mood-normalizers (39), Post's formulations, which linked a proposed mechanism of action with prophylactic effects, inaugurated a new era of mood-stabilization, although the concept was nevertheless slow to take shape – the term mood-stabilizer in fact only appears sporadically in the literature until the early to mid-1990s.

As this new concept took shape, the proposed effect of mood-stabilizers was relatively disease-specific and furthermore was one that should occur regardless of any beneficial non-specific functional effects such agents might also have. In addition, it followed from Post's proposals that the longer the period the person was left untreated and the greater the number of episodes they had the greater the propensity to future episodes would be. This conceptualization coincided with contemporary thinking about lithium and it mandated early intervention. Evidence that valproate had similar mood stabilizing properties to carbamazepine appeared to endorse the kindling hypothesis.

The kindling model put a premium on investigating other anticonvulsants. Beneficial psychotropic effects in patients being treated for epilepsy, echoing those previously seen with valproate and carbamazepine, were also described for lamotrigine, gabapentin, vigabatrin and other anticonvulsants. However, not all anticonvulsants appear to be of benefit in manic-depressive disorders. The current status of gabapentin is uncertain (40), and it would seem that vigabatrin is unhelpful, tiagabine may be of limited utility and topiramate is not routinely helpful, although it may have some utility in refractory cases.

The findings that some anticonvulsants have minimal effects for mood disorders suggest that the notion that agents that reduce kindling will necessarily be beneficial in manic-depressive orders needs to be reviewed. One possibility is that agents

with selective effects on limbic systems will be found to be useful, whereas others will not. An alternative, however, is that these differences in efficacy may be parsimoniously explained in terms of differential functional effects of lithium, carbamazepine, valproate, valpromide and lamotrigine.

While slow to emerge, the notion of mood-stabilization has all but replaced the earlier notion of prophylaxis. If we ask whether any of the newer mood-stabilizing agents can be demonstrated to be truly prophylactic, we reach the paradox at the heart of the mood-stabilization debate. Mood-stabilizers are agents, which ideally would show prophylactic effects without evidence of benefits in the acute state. However, current 'mood-stabilizers' are only on the market because of demonstrable benefits in acute states.

This sets up a number of paradoxes. Antipsychotics and antidepressants demonstrably produce treatment effects in the depressive and manic poles of bipolar disorder. Chlorpromazine was first used in the management of mania and neuroleptics have been the standard agents for the management of manic states ever since. If by an antidepressant is meant an agent that demonstrates a treatment effect in a trial with depressed patients, then most neuroleptics are antidepressants (41), although it should be noted that despite this evidence of short-term effects, few clinicians would regard these agents as antidepressants in the longer run. These findings in fact may do more to demonstrate the pitfalls of short-term trials than anything else. The functional effects that these agents produce have face validity as therapeutic principles in the management of both depressive and manic states.

Indeed ironically, while antidepressants may cause manic reactions, one of the only controlled trials done of imipramine in mania demonstrated that it had beneficial effects in some patients (39). It was a consideration of results such as these in fact that led Schou to the concept of a mood normalizer in 1963.

Mood or psyche stabilizers?

The dominant conception of a mood-stabilizer at present appears to be that such a drug attacks a specific underlying physiological abnormality without necessarily producing any obvious functional effect. The implication is that all mood-stabilizers are in some way modifying the same mechanism. Secondary messengers appear to be the favorite target at present, but there are no common specific effects reported to date.

While this conception can draw on historical notions about the specificity of lithium, the

subsequent history of lithium as well as the discoveries of the first psychotropic properties of valpromide and carbamazepine point to a need for a new term such as a psycho-stabilizer. The standard model is now a nosolytic one, in which benefits are specific and nosolytic. A psycho-stabilizer, in contrast, would produce a serene, sedative or anti-irritability effect that would have demonstrable benefits across a range of syndromes.

The literature on lithium culminating in Sheard's 1971 trial now suggests that far from being specific for manic-depressive illness lithium may be an agent that among other things reduces the sensitivity to events in the environment so that the disruptive impact of these events on internal mood states is minimized. Such an effect has a clear functional utility that conceivably could produce benefits across a range of psychosyndromes, other than manic-depressive illness. Carbamazepine and valproate appear to produce somewhat different but broadly serene effects. For this alternative model to attract support it would be necessary to specify the differences between these agents and lithium in sufficient detail to account for the conventional clinical wisdom and trial evidence that carbamazepine and valproate may be more useful than lithium for mixed mood disorders and less beneficial in classic manic-depressive illness. This latter formulation of course stems from a period when lithium was viewed of as being all but specific to manic-depressive illness in a way that was never the case for carbamazepine or valproate.

Some specification of differential functional effects is possible. Valpromide and valproate were discovered initially through their use in mania and because of their particular 'sedative' properties. Sedation is a therapeutic principle that makes sense in the management of manic states. Lamotrigine in contrast appears to be more effective in the depressive poles of manic-depressive disorder and this is an agent that far from being sedating is more likely to be described in terms of its euphoriant properties (42). There is some basis therefore for arguing that lithium, carbamazepine, valproate and lamotrigine all have functional effects that have face validity in terms of managing various phases of manic-depressive disorders. The implication of this formulation however is that while these agents are now thought of as being a homogenous group, they may in fact be quite diverse agents all of which have a certain utility when used judiciously in manic depressive states.

Psychotropic utility and psychotropic efficacy

Recently two further conceptual issues have been raised in the domain of mood disorder therapeutics.

First, in addition to the possible deleterious effects of antidepressants on bipolar mood disorders, the possibility has also been raised that antidepressants may have equally problematic effects in the unipolar domain. Fava in particular has argued that antidepressants while efficacious in resolving acute disorders may in fact lead to further episodes by a sensitization process (43).

A related area of interest in the treatment of unipolar disorders has lain in the notion that treatment should aim at restoring well-being rather than simply ameliorating the main features of acute episodes. This domain links to the issue of relapse to antidepressants in that the existence of subclinical or residual symptoms is the biggest single predictor of future relapse (44).

In a study that bears on both these points Tranter et al. (45) have recently provided evidence that subjects may be constitutionally predisposed to respond optimally to agents selective to particular systems and that these agents have distinctive functional effects. The implication of these data is that individuals may respond less well if at all to agents acting primarily on the wrong system for them. Such sub-optimal responses can be expected to be more likely to lead to further illness episodes than would optimal responses. There is no reason to believe that similar considerations will not also apply to the mood-stabilizers.

Perspectives for the future

A number of consequences stem from the above formulation. It has proven all but impossible to demonstrate prophylactic efficacy for agents, other than perhaps lithium, in the case of manic-depressive disorders. A proper trial demonstrating such effects would run for many years and would demonstrate a reduced frequency of episodes, an increase in the inter-illness interval compared with placebo and would also demonstrate that these effects outweigh any disruption produced by withdrawal syndromes on discontinuation. In practice it has proved impossible to sustain a seriously ill patient group in such a trial.

However another method of evaluating treatments opens up if the focus switches to their more immediate functional effects. If patients on any of these agents identify a specifically useful effect produced by that agent, this would *de facto* produce a rationale for continuing treatment with that agent in that particular person. Trials could conceivably compare outcomes in patient groups who could identify beneficial functional effects compared with those who could not do so. The ultimate benefits of such an approach however will

depend critically on practitioners identifying useful 'psyche stabilizing' effects in an individual and proceeding with treatment on this basis rather than treating on the basis that the agent has supposedly been demonstrated to be a mood stabilizer and therefore will be beneficial regardless of whether the taker describes beneficial functional effects.

In summary, there would seem to be few good experimental or theoretical grounds to think that 'mood-stabilizers' target the underlying deficit in mood disorders any better than the previous generation of antidepressants or neuroleptics. In other words, the response of patients with mood disorders to anticonvulsants is simply not the same as the response of epileptic patients to anticonvulsants. But there are abundant clinical and historical grounds to think that 'mood-stabilizers' have comparatively unexplored psychotropic effects that might well account for their apparent benefits in both acute and non-acute phases of bipolar disorders. Work is needed to specify these effects and to match therapeutic effects to patient types.

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Insert 'superior' character	/ through character or ⤴ where required	⤴ under character e.g. ⤴
Insert 'inferior' character	(As above)	⤵ over character e.g. ⤵
Insert full stop	(As above)	⦿
Insert comma	(As above)	,
Insert single quotation marks	(As above)	⤴ and/or ⤵
Insert double quotation marks	(As above)	⤴ and/or ⤵
Insert hyphen	(As above)	Ⓜ
Start new paragraph	⤴	⤴
No new paragraph	⤵	⤵
Transpose	⤴	⤴
Close up	linking ⦿ letters	⦿
Insert space between letters	⤴ between letters affected	#
Insert space between words	⤴ between words affected	#
Reduce space between letters	⤴ between letters affected	⤴
Reduce space between words	⤴ between words affected	⤴