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Commentary

"Mood-stabilizers: the archeology of the concept" – by M Harris, S Chandran, N Chakraborty and D Healy: a commentary

Paul Grof. "Mood-stabilizers: the archeology of the concept" – by M Harris, S Chandran, N Chakraborty and D Healy: a commentary. Bipolar Disord 2003: 5: 453–455. © Blackwell Munksgaard, 2003

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I find two important tenets in the Harris et al. paper. First, a call for reconsideration of the current concept of a 'mood stabilizer', both for historical reasons and because the substances currently used in the long-term treatment of bipolar disorders lack pharmacotherapeutic specificity. Secondly, a proposal to search for matching between patient characteristics and a successful outcome of the treatment with each substance.

The criticism of the loose use of the term 'mood stabilizer' has been mounting; it has already been raised by several other authors (e.g. 1, 2). Professor Guy Goodwin, for example, has pointed out that, rather than clarifying what mood stabilization should be, the term has been repeatedly used to accommodate the use of several anticonvulsants in the long-term treatment of bipolar disorders. Harris et al. remind us that this broadening of the concept of 'mood stabilizer' was supported by both the pharmaceutical industry, searching for a wider pool of consumers for their products, as well as by psychopharmacologists heavily invested in bipolar drug trials.

The Harris et al. article stresses that introducing lithium as the first mood stabilizer was partly based on the wrong assumption that lithium's benefits were specific for a mood disorder: manic depressive illness. Studies that followed the initial discoveries (3–5) have shown, however, that besides the dramatic prophylactic effect of lithium in episodic bipolar disorders, lithium can also be useful in several other psychiatric and medical conditions. An effective antimanic agent, lithium can also reduce aggressive behavior, treat depression and 'augment' antidepressants, improve selected schizoaffective and schizophrenic disorders, and be useful in medical conditions such as low white blood count, hyperthyroidism and cluster headaches (6).

To eloquently point out the historical complexity behind the development of the medications currently used in the long-term treatment of bipolar disorders, Harris' co-author Healey capitalized on his extensive study and knowledge of the history of psychopharmacology, so well documented in his books on the subject (e.g. 7). The mood-improving properties of carbamazepine and valproic acid have indeed been initially observed a number of years ago, the pioneering previews taking place during the same decade as the initial lithium reports. The historical contexts and connections Harris et al. describe are truly amazing. Looking back, it is fascinating to read which idiosyncratic circumstances led to the early use of carbamazepine in Japan and valproic acid in France and Germany.

It is interesting to note that the term 'mood stabilizer' became wide-spread only when a pharmaceutical company started the aggressive marketing of valproic acid for bipolar disorders in the early 1990s. And the pharmaceutical companies' interest in the area of bipolar disorders has played its part in sustaining wider interest in the concept.

As Harris et al. point out, two assumptions played a major role in making the usage of the term 'mood stabilizers' so popular: the idea of the relatively disease-specific effects of 'mood stabilizers' and their link with the kindling hypothesis. Interestingly enough, a closer look suggests that none of these assumptions has been adequately justified. None of these substances, including lithium, is specific for a particular mood disorder, and clinical data contradict the explanation of the course of most bipolar disorders by the kindling hypothesis. In addition, as only the minority but certainly not all anticonvulsants appear to be of benefit in bipolar disorders, the concept that agents that reduce kindling would necessarily be beneficial in bipolar disorders needs to be revised.

Harris et al. make a strong and well-argued case for revisiting the 'mood stabilizer' concept and for not using it loosely. Several definitions of mood stabilizers have been proposed, leading to confusion, as several authors have already discovered (1, 2). Harris et al. point out that nearly all the substances currently labeled as 'mood stabilizers' have only shown demonstrable benefits in acute states, and not in long-term treatment (this was true when their article was written but is slowly changing). In contrast, the authors logically formulate what is so far the most radical, potential definition of mood stabilizer: ideally an agent which shows prophylactic effects while evidence of benefits in the acute states is not needed. Such a definition would be in stark contrast to those definitions previously proposed, as they consider antidepressant and antimanic effects as the pillars of 'mood stabilization'. Harris et al. correctly point to the number of paradoxes that may arise if a definition of a mood stabilizer is imprecise, based mainly on the benefits for depression and mania: most neuroleptics such as chlorpromazine and haloperidol must then be considered mood stabilizers as, according to the old literature, they have demonstrated significant treatment effects with both manic and depressed patients. Similarly antidepressants, such as imipramine, have in the past been reported as effective against depression and mania in clinical trials, and should thus fall under the umbrella of a 'mood stabilizer'.

Two other intriguing thoughts in the article are worth noticing. First, Harris et al. point out the interesting implication of the current concept: that all 'mood stabilizers' effective in the same disorder should in some way modify the same underlying neurobiological mechanism. This implication contrasts with the growing evidence that bipolar responders to one monotherapy have usually failed on the other 'mood stabilizers' (e.g. 8, 9). The article also raises the important point that the differential effects of lithium, carbamazepine, valproate and lamotrigine, acting on various phases of manic depressive disorders, attack the wide-spread assumption that bipolar illness is a single entity.

I have had difficulty with the statement of Harris et al. that 'in practice it has proved impossible to carry out proper trials of new substances demonstrating prophylactic effects'. I think the methodology has been worked out over many years (10) and proper prophylactic trials are possible, just damned difficult and very expensive.

Harris et al. conclude with constructive proposals. Both past and present indicate that the definition of 'mood stabilizer' must be re-thought. In the meantime, positive treatment outcomes should be matched with certain patient characteristics, in order to improve the selection of an effective treatment. This type of research has in fact already been underway and while the Harris et al. manuscript has been in revision, some findings have appeared and suggest the characteristics of lithium, lamotrigine and atypical neuroleptic responders (11, 12).

Overall, the manuscript demonstrates again that there is value in learning from history and that knowing the past often leads to clearer thinking about present problems.

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