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EDITORIAL REVIEW

What is a mood stabilizer?

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ABSTRACT

The concept of mood stability is attractive to both patients and clinicians alike, and hence the term 'mood stabilizer' has widespread currency. However, its worldwide acceptance and use in clinical practice is at odds with the absence of official recognition by regulatory authorities. The ideal mood stabilizer is said to have efficacy in the treatment of acute manic and depressive episodes, and also be effective in the prevention of recurrences. However, in reality, few drugs with perhaps the exception of lithium, come close to this gold standard; yet many agents aspire to the title, and some have arguably achieved it prematurely. It is, therefore, important to reconsider the definition of a mood stabilizer and critically review which agents, if any, satisfy the necessary eligibility requirements by reference to reasonable criteria and comparator data. The term mood stabilizer is an important label. It needs to be applied judiciously because it confers clinical credibility and qualifies long-term use in maintenance and prophylaxis. It is also important with respect to developing guidelines for treatment and the further development of novel agents. Most importantly, however, it is a term that is innately appealing because of what it promises: for this reason alone it should encompass only those agents that can deliver.

Introduction

There is no generally accepted definition of the term 'mood stabilizer', and regulatory authorities such as the US Food and Drug Administration do not formally recognize its existence. It was probably first used in its contemporary sense to describe lithium, but the original published description of chlorpromazine's actions referred to 'un nouveau stabilisateur neurovégétatif'(Laborit *et al.* 1952) so related forms of words have been around from the birth of modern psychopharmacology. The term has now come to encompass a number of anticonvulsants and antipsychotics. Indeed, its use has been at times indiscriminate, resembling the misuse of other words in psychiatry, for which the Humpty Dumpty principle applies: 'it means exactly what I choose it to mean – neither more nor less' (Lewis Carroll, 1998)

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Definition of a mood stabilizer

Terminological exactitude has never been a strong suit of pharmacology, because pharmacology is about relevant drug action. Ideally, this can be specified at the level of a fundamental chemical interaction. If this is known, then all medicines with similar actions will form a class. It is often now possible, from the initial development of a new compound with actions on a specific receptor, to predict their class and likely clinical indication. However, in the history of psychopharmacology, effects of medicines have been observed clinically before their molecular action was remotely understood – hence our medicines were called neuroleptics, antidepressants and anxiolytics. Subsequently, work on what these compounds actually do has

given us a next generation of medicines informed by rational pharmacology – dopamine receptor antagonists, selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NARIs) and gamma-aminobutyric acid (GABA) receptor agonists of various kinds. The identification of a clinical action was the stimulus to a refined understanding, and like any detective work, which such science resembles, a range of ideas and experiments were brought to bear in producing answers. However, in the case of lithium we have not yet seen the rational clinical development of a new chemical entity with comparable molecular actions. Instead, we have incomplete analogy as the driver for innovation. Therefore, the anticonvulsants were initially tried in bipolar disorder on the basis of a hypothesis that instability of mood and seizure disorders may have some fundamentals in common. A similarly incomplete theory, linking mania to dopamine and depression to serotonin, may also be emerging to justify thinking of the atypical antipsychotics as mood stabilizers (Malhi *et al.* 2005). However, in neither case is there clinching evidence linking drug action to pathophysiology. Accordingly, class effects of mood stabilizers, if they exist, cannot yet be defined at a molecular or even physiological level. They must still be measured against a pragmatic definition of clinical efficacy, like the original psychotropic medicines. In this editorial review we discuss the competing definitions that have emerged in recent years and what value the term currently has.

Effective in treating acute mania and depression

For most psychotropic agents, acute efficacy tends to parallel effects in relapse prevention. Therefore any treatment effective in treating acute episodes of mania and bipolar depression might be expected to have efficacy in maintenance. However, acute and long-term actions do not necessarily correlate. Indeed, by selecting for actions in acute situations one might miss significant long-term benefits. In epilepsy, this is now believed to be the case for some anticonvulsants, for example, levetiracetam, which was active only in unconventional animal models. The more conventional assays selected the ability to suppress paroxysmal events and resulted in the discovery only of agents that inhibit neuronal excitability. In bipolar disorder, semi-analogously, preliminary evidence suggests that some psychological interventions have efficacy in the maintenance and prophylaxis of bipolar depression (Lam *et al.* 2003; Colom *et al.* 2003) but may not be effective when patients are acutely unwell or very recurrent (Scott *et al.* 2006). Conversely, what definitely works acutely, may rarely be satisfactory in the long term because of side-effects or safety concerns. This applies to electroconvulsive therapy (ECT) and potentially to other medicines including the atypical antipsychotics (see below). However, it is important to note that maintenance ECT has its advocates and is arguably useful in cases where all else has failed.

Effective in stabilizing rapid cycling mood

Rapid cycling bipolar patients are characterized by an accelerated illness course that is often more difficult to treat and less likely to show a prophylactic response to lithium (Dunner & Fieve, 1974). Thus, any medicine that achieves efficacy in rapid cycling patients probably satisfies the highest possible standard for a mood stabilizer. Trials in these patients could provide a rapid proof of concept in drug development. However, the term 'rapid cycling' actually subsumes more than one pattern of illness: it requires four or more 'episodes' in the preceding year, but these may occur as discrete manic, mixed or depressive episodes with mood stability in the intervening intervals, or as continuous cycles. Furthermore, episodic or continuous cycling can occur in patients with bipolar I, bipolar II and spectrum disorder. Hence rapid cycling mood is a heterogeneous phenomenon and positive responses may reflect differential efficacy in different subgroups. In practice, this has rarely been examined, although in the case of lamotrigine, an overall benefit compared with placebo was seen because of a differential effect in bipolar II patients, not seen in bipolar I (Calabrese *et al.* 2000). Interestingly, a recent study failed to show greater effectiveness for divalproex compared to lithium in the long-term management of rapid-cycling bipolar disorder (Calabrese *et al.* 2005*b*). Thus, to accept an effect in a subgroup may be too liberal, while to insist upon unusual efficacy in

all rapid cycling patients may set the bar too high for otherwise useful treatments.

Effective in the extended treatment of mania or depression without worsening the other pole of the illness

In this definition, retention of the gains obtained during acute treatment is emphasized instead of prevention of a new episode of illness in euthymic individuals. In unipolar depression, the definition of treatment phases is largely (and sensibly) based on the timing of pragmatic clinical decisions about discontinuation of treatment (Frank *et al.* 1991); treatment phases are thus: acute, continuation (to prevent relapse), and maintenance therapy (to prevent recurrence). In bipolar disorder, this terminology may be applied to first-onset or early episodes, but the distinction between relapse and recurrence is increasingly unconvincing, either as the illness progresses to more frequent episodes, or outcomes become more complex, with subsyndromal depression, mood instability, the development of a mixed state, or rapid cycling. Nevertheless, a distinction can be made between medicines used specifically for acute and continuation effects (short term), which it is intended to stop, and those used for maintenance therapy (long term) where the intention to treat is indefinite. Separating treatment in this manner may be helpful because, given the chronic nature of bipolar disorder there is a tendency to regard all treatment as long term. This probably promotes exotic polypharmacy – already a major concern (Frye *et al.* 2000). Clearly, mood stability should be a stated objective for both short- and long-term use of medicines.

In practice, adequately controlled extension studies are difficult because they imply holding a control group on placebo for 12 weeks or more. In mania, placebo phases are usually 3–4 weeks and in depression 6–8 weeks. The subsequent definition of recovery 'without worsening the other pole of the illness' has very rarely been observed with placebo control and no published articles yet exist. Head-to-head comparisons of active agents would also be informative but have rarely been conducted independently. Consequently, we are simply uncertain whether one acute anti-manic treatment is more or less likely than another to be associated with, say, a switch to depression in the extension phase of treatment. Hence, as a definition, 'to be effective in extended treatment' currently offers no practical advantages over the alternatives, although it is a property one would like to see in all phases of effective treatment.

Effective in preventing recurrence of mania and depression

This definition reflects the traditional concept of maintenance therapy involving long-term treatment to prevent new episodes of mania and depression. As the old term 'prophylaxis' implied, it was often reserved for those cases, usually treated with lithium, in whom euthymia was fully achieved and maintained over many years. Arguably, remaining well and preventing further episodes is the most important aspect of managing bipolar disorder. We also have the largest number of relevant trials in this category.

To establish efficacy, there are a variety of possible trial designs. A true maintenance study would take fully recovered patients, treated with medicines other than those under investigation (and preferably discontinued) and randomize patients to the medicine of interest or placebo (and/or a comparator). In fact there have been virtually no trials of this kind. Instead relapse prevention studies tend to recruit patient groups who both show an acute treatment response and tolerate the medicine of interest in a phase of open treatment. They are then randomized to continue or withdraw from the treatment. The time to relapse in differently treated groups is the measure of effect. Trials of this kind have been successfully completed for lithium (Geddes *et al.* 2004), olanzapine (Tohen *et al.* 2003) and lamotrigine (Calabrese *et al.* 2003) with the former two more effective in preventing manic relapse and lamotrigine more effective in depression.

The existing trials have taken different approaches to the acute open treatment phase. To a greater or lesser extent most trials of this kind 'enrich' with patients who are compliant with a protocol, tolerant of the medicines under investigation and responsive to their acute effects. This is no bad thing, since it reflects the treatment question – to continue or not? – that arises in ordinary practice, and increases the efficiency of the study to detect a meaningful

difference. However, comparison of response rates between studies is potentially misleading. Moreover, this design risks discontinuation effects – where relapse is provoked by withdrawal of the treatment. This, for example, occurs with lithium unless it is tapered over longer than 2 weeks (Goodwin, 1994). Withdrawal relapse is putatively indicative of efficacy but it is likely to magnify the true size of the treatment effect.

Class effects

In the management of bipolar disorder lithium occupies a unique position, however, a number of drugs that have similar primary actions are grouped into 'families' that perhaps exert a class effect. Two such groupings are the more established anticonvulsants and the newly formed atypical antipsychotics.

Anticonvulsants

Two decades ago carbamazepine was used only in specialized cases of bipolar disorder and usually for treatment of refractory illness, whilst valproate was about to be studied in mania. In the treatment of acute mania Okuma *et al.* (1979) reported in favour of carbamazepine over chlorpromazine and a trend for superiority in a 1-year prophylactic study (Okuma *et al.* 1981). The discovery that carbamazepine, and then valproate, are valuable in treating bipolar patients grew out of a heuristically valuable hypothesis that kindling in epilepsy has important parallels with the evolution of bipolar disorder (Post *et al.* 1983). We still do not know whether this hypothesis is better than a metaphor: the efficacy of the anticonvulsants is the best evidence that it is.

Where anticonvulsants share basic mechanisms of action with existing compounds, then this may form the basis for classification as mood stabilizers by extrapolation from the verified clinical actions of the best-characterized exemplars. However, the potential for mood-stabilizing properties in really novel anticonvulsants merits investigation at an early stage in their commercial development. Anticonvulsants have a variety of cellular actions and we are seeing differentiation and partitioning of their effects in bipolar disorder (Harwood & Agam, 2003). It remains a possibility that the pharmacology of the anticonvulsants may yet help to distinguish cellular mechanisms contributing to different aspects of bipolar pathophysiology. But it is already inappropriate to lump all the anticonvulsants together as equally useful in bipolar disorder since gabapentin and topiramate have failed to demonstrate acute efficacy.

Atypical antipsychotics

More pragmatic arguments apply to the atypical antipsychotics, such as olanzapine and quetiapine, which have demonstrated significant efficacy in the management of acute mania, depression and relapse prevention (Tohen *et al.* 1999; Calabrese *et al.* 2005*a*; Malhi *et al.* 2005). Several may eventually satisfy the criteria for a mood stabilizer and to assume a class effect is tempting. It is interesting from a pharmacological perspective that actions on dopamine and serotonin function may be central to efficacy. However, safety concerns about these compounds as long-term treatments are also rising, with the increased awareness of their potential metabolic complications.

Treatment guidelines

Use of the term 'mood stabilizer' has been driven in part by the prejudices enshrined in important US guidelines. In an influential early version, a group of up to 100 US experts recommended the use of a 'mood stabilizer' (then meaning lithium or valproate first line, or sometimes carbamazepine) in all phases of the illness (Frances *et al.* 1996, 1998). The guidelines also implied that initiating treatment of an acute episode should always be regarded as the start of maintenance therapy. In this formulation, antipsychotics and benzodiazepines were regarded as adjunctive treatments, not for long-term use. The elevation of valproate to equivalent status with lithium was not evidence based, although it had been shown to be effective in mania. The de-emphasis of antipsychotics simply ignored usual practice – first-line use for severe mania; it occurred largely because of the risk of tardive dyskinesia, with long-term use. These recommendations conflicted with practice in the rest of the world.

If guidelines are to have clinical salience and effect they need to be based on, and remain within, the best available reliable evidence (e.g. Goodwin *et al.* 2003). United States guidelines transgressed this boundary and by doing so

assigned commercial value to any medicine described as a mood stabilizer. However the emphasis on a treatment strategy based on 'mood stabilizers' had an upside: it prompted clinicians to think about both poles of the illness in all phases of treatment. This remains a useful imperative.

Conclusions

The term 'mood stabilizer' is common currency and is used impressionistically by clinicians and researchers alike. If we employ its strictest definition, proposed by Bauer & Mitchner (2004) – prophylaxis and the prevention of recurrence *and* evidence of short-term efficacy for both poles of the illness – lithium probably meets the criterion, but only just (and so does olanzapine, although its clinical experience is obviously much less). Therefore, for any agent to be called a mood stabilizer, we probably need to know how it performs in comparison to lithium. We also need to be able to gauge its relative effects against the manic and depressive poles of the illness. However, academic arguments about technical meaning may miss the point. Mood stability is an aspiration that patients, their families and attending doctors probably share and if a medicine were to assist in achieving this ultimate goal, then doctors are more likely to prescribe such a treatment and patients are more likely to take it. Put simply, the term mood stabilizer sounds comforting and may reflect our fond and perhaps somewhat naive hopes. Accordingly, it will also more effectively convey a marketing message. Indeed, all well-chosen words may be susceptible to echoes of such hidden persuasion, and it may not be bad that they do. However, Lewis Carroll's understanding of linguistic philosophy seems almost to have anticipated the commercial pressures we need to understand and often resist: When I make a word do a lot of work like that,' said Humpty Dumpty, 'I always pay it extra' (Lewis Carroll, 1998).

Declaration of Interest

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