Re-evaluating carbamazepine prophylaxis in bipolar disorder

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The recent meta-analysis of Dardennes *et al* (1995) and a previous letter in the *Lancet* (Murphy *et al*, 1989), both concerning carbamazepine in bipolar affective disorder, suggest there are inadequate data, on the basis of the several studies reviewed, to support the claim that carbamazepine has prophylactic efficacy in the treatment of bipolar illness. While this suggestion may be correct based on the limited data selected for inspection and discussion, a wealth of other data more strongly suggest the clinical efficacy of carbamazepine in the acute and prophylactic treatment of bipolar patients.

Carbamazepine is approved in 107 countries for use in affective illness, yet the only drug approved in the USA by the Food and Drug Administration (FDA) for long-term prophylaxis in bipolar illness is lithium carbonate (although valproate has just been approved for the treatment of acute mania). There is increasing recognition that up to 50% or more of patients with bipolar illness are inadequately responsive to long-term lithium treatment (O'Connell *et al*, 1991; Vestergaard, 1992). Thus, the clinician is obligated to find treatment alternatives, even among drugs not yet approved for bipolar illness, such as carbamazepine.

ADDITIONAL SUPPORTING EVIDENCE OF CARBAMAZEPINE EFFICACY

We have summarised in Table 1 at least 14 controlled or partially controlled studies of carbamazepine in long-term prophylaxis. While some of these studies utilise very different types of statistical designs, and have been criticised for their methodological and statistical flaws (Prien & Gelenberg, 1989; Dardennes *et al*, 1995), as a whole they are strongly supportive of the efficacy of carbamazepine in the affective disorders.

Table 1 Controlled and partially controlled studies of carbamazepine (CBZ) and oxcarbazepine prophylaxis in affective illness

Study	Design	Placebo	CBZ responders		Lithium responders	
			n	% response	*n*	% response
Ballenger & Post (1978)	Double-blind, mirror image		6/7	86	(-)	(-)
Post *et al* (1983)						
Okuma *et al* (1981)	Double-blind	2/9	6/10	60	(-)	(-)
Svestka *et al* (1985)	Randomised		14/24	62	12/24	50
Kishimoto & Okuma (1986)	Cross-over		(-)/18	Fewer hospitalisations *v.* lithium	(-)	(-)
Cabrera *et al* (1986)[1]	Randomised		2/4	50	3/6	50
Placidi *et al* (1986)	Double-blind, randomised		21/29	72	20/27	74
Watkins *et al* (1987)	Double-blind, randomised		16/19	84	15/18	83
Elphick *et al* (1988)	Double-blind, randomised		3/8	37	8/11	73
Lusznat *et al* (1988)	Double-blind, randomised		(-)/9	Fewer depressive episodes	(-)/5	(-)
Bellaire *et al* (1990)	Randomised		34/40	85	42/49	86
Di Costanzo & Schiffano (1991)	Randomised[2]		(-)/16	Fewer depressive episodes with lithium+CBZ than lithium alone	(-)/16	(-)
Mosolov (1991)	Randomised		(-)/30	58[3]	(-)/30	54
Coxhead *et al* (1992)	Double-blind, randomised		7/15	47	7/16	44
Denicoff *et al* (unpublished observations)	Double-blind, randomised		11/35	31	14/42	33
All controlled/partly controlled studies			120/191	63	121/193	63
All open studies			390/629[4]	62		

(-), not stated.
1. Oxcarbazepine.
2. Pseudo-randomised to lithium *v.* CBZ+lithium; greater antimanic and antidepressant efficacy in first year *v.* lithium alone.
3. Expressed as percentage decrease in number of episodes.
4. Includes carbamazepine combination therapies.

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Moreover, the data in these controlled or partially controlled studies, either double-blind or randomised, indicate that 63% of patients show moderate to marked response, similar to the 62% response rate in the more substantial open clinical trial literature. Prien & Gelenberg (1989) also indicated that the parallel design studies of Placidi *et al* (1986), Watkins *et al* (1987) and Lusznat *et al* (1988) utilised in the assessment of carbamazepine efficacy were flawed and less convincing than some other types of studies. Prien & Gelenberg (1989) and Grof (1994) suggest that mirror-image designs in treatment-refractory patients, and other double-blind designs using on–off–on methodologies, do in fact support the efficacy of carbamazepine.

For example, in our double-blind studies with carbamazepine, we documented repeated clinical improvement during long periods of blind carbamazepine administration; exacerbation of mania, psychosis and time in seclusion with placebo substitution; and renewed response with blind carbamazepine re-institution (Ballenger & Post, 1978; Post *et al*, 1983; 1984). The mirror-image design used in our later report (Post *et al*, 1990) also indicates that in many treatment-refractory patients, carbamazepine used alone or as an adjunct to previously ineffective medications (Denicoff *et al*, 1994) can make a notable difference in patients' clinical course, although some patients do show loss of response to carbamazepine (or the other mood stabilisers, lithium and valproate) during long-term follow-up in a pattern resembling tolerance (Post *et al*, 1990; 1996, in press).

Elsewhere, we have summarised data from 19 double-blind studies utilising several types of designs (Post *et al*, 1996, in press) supporting the acute anti-manic efficacy of carbamazepine or its keto-congener oxcarbazepine. In our studies and those of six others, carbamazepine showed generally comparable magnitude, time-course and percentage of response to those of neuroleptics. Moreover, in our series, 18 of 19 patients receiving a second double-blind clinical trial of carbamazepine at the NIMH using a placebo–active–placebo–active design showed an adequate response during the second trial (Post *et al*, unpublished data), further confirming the initial observations of clinical efficacy using on–off–on designs. The question of whether carbamazepine is effective in the treatment of some patients with affective disorders can thus be answered more affirmatively on the basis of this additional literature.

RESPONSIVE SUBGROUPS: THE IMPORTANCE OF IDENTIFYING PREDICTORS OF RESPONSE

The more important questions would now be the response rate to carbamazepine in different clinical subgroups, and whether individual clinical or biochemical markers could be used to predict or increase the likelihood of response. For example, preliminary evidence suggests that a pattern of cerebral hypermetabolism (particularly in the temporal lobes), but not the more typical frontal hypometabolism pattern in depression, is associated with antidepressant response to carbamazepine (Ketter *et al*, 1996). If provided with better estimates of likelihood of response, the clinician could more accurately assess the risk:benefit ratio of using carbamazepine for the treatment of bipolar illness, which, if inadequately treated, carries a lifetime mortality rate from suicide of 10–20%. In contrast, serious side-effects of carbamazepine, such as agranulocytosis and aplastic anaemia, have been estimated to occur in only 1 in 10 000–120 000 patients (Pellock, 1987).

IMPLICATIONS FOR CLINICAL THERAPEUTICS

A similar argument could be made for the clinical use of the mood-stabilising anti-convulsant valproate in prophylaxis of refractory bipolar patients. While there are virtually no controlled studies of this drug's long-term efficacy, a substantial clinical literature using open studies suggests that it does have important effects in preventing manic and depressive recurrences in patients with rapid cycling and other extremely refractory presentations, including those patients with dysphoric mania (Emrich *et al*, 1980; Lambert, 1984; McElroy *et al*, 1992; Calabrese *et al*, 1993; Jacobsen, 1993; Schaff *et al*, 1993). These complement the controlled studies in acute mania leading to the FDA's approval of valproate for this indication (Bowden *et al*, 1994).

Here the interpretation of Dardennes *et al* (1995) regarding carbamazepine becomes crucial for clinical therapeutics. Are Dardennes *et al* suggesting that, because carbamazepine has not met their pre-selected criteria for efficacy, this agent should not be used in the treatment of recurrent bipolar disorder based on the available evidence? We would submit, on the contrary, that continued use of the approved drug lithium as the only mood-stabilising drug approach to patients not adequately responsive to it, would constitute a grievous clinical error. These clinical considerations should, perhaps, be integrated with the opinion that while one type of pre-selected clinical trial methodology has failed to meet one academic standard for the demonstration of efficacy (although other types of designs have unequivocally demonstrated efficacy within individual patients: Ballenger & Post, 1978; Post *et al*, 1983; 1984; 1990), promising treatments should not be withheld from patients on the basis of this partial approach to the available data. This opinion would be in accordance with the 1994 American Psychiatric Assocation guidelines for treatment of bipolar illness (Hirschfeld *et al*, 1994) and with most other clinical review panels and authorities in the field.

Hopefully, the academic aspects of this argument will be used not to limit treatment options but to propel further studies of not only the efficacy of the range of mood stabilisers in bipolar illness, but also of their optimal selection based on patients' clinical and biological presentations, and their appropriate application to clinical therapeutics in both monotherapy and rational combination therapy.

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