Doses of carbamazepine and valproate in bipolar affective disorder

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Carbamazepine and valproate are now well established treatments for bipolar affective disorder (BAD). Both drugs are used in the acute treatment of mania and, more frequently, as longer-term mood stabilisers. The *British National Formulary* (*BNF*, Vol. 32, 1996) provides information on the use of carbamazepine in the 'prophylaxis of manic depressive illness' and suggests that the 'usual range' of doses is between 400 mg and 600 mg daily. No guidance on the use of valproate in BAD is given in the *BNF* because the drug is not licensed for this indication in the UK.

Perhaps because of the absence of firm prescribing advice for either drug, the doses of carbamazepine and valproate seen in practice vary considerably. In general, low doses appear to be most frequently prescribed and daily doses above 600 mg of either drug are not often seen. Doses seem to be only rarely titrated to maximise efficacy. This is possibly because the evaluation of efficacy in preventing mood changes (prophylaxis) takes months or even years.

It is apparent that more specific guidance on the dosing of carbamazepine and valproate would prove valuable and so we have examined pertinent research data in an attempt to develop more useful advice.

Table 1 lists details of important trials of carbamazepine and valproate in mania and BAD (retrieved from MEDLINE search, July 1996 and examination of reference sections of these papers). It can be seen that plasma level monitoring was used in all studies. With carbamazepine, levels above 7 or 8 mg/l were generally associated with efficacy. With valproate, levels within the range 50–100 mg/l appear to be related to response. There are two exceptions to these general observations. Stuppaeck *et al* (1990) noted that a mean level of 5.7 mg/l carbamazepine gave an 80% response rate in their cohort, but it is noteworthy that only seven of 25 patients had true BAD. Jacobsen (1993) showed that low levels of valproate (mean 32.5 mg/l) produced a sustained response in patients with milder forms of BAD and other disorders.

The doses of carbamazepine used were somewhat higher than those recommended by the *BNF*: mean daily doses ranged from 614 mg to 1400 mg. Indeed, in practices where a target plasma level of 7–12 mg/l is used, daily doses average 1000 mg (Gerner & Stanton, 1992).

With the exception of the Jacobsen study, patients in valproate trials usually received doses considerably in excess of 750 mg/day. In a selection of smaller trials reviewed by McElroy and co-workers (1992), valproate doses were of a similar magnitude and the authors felt strongly that 50 mg/l was the threshold plasma level for response.

The heterogeneity of the studies, subjects and conditions described in Table 1 makes any meaningful conclusion difficult. In addition, few of these trials attempted to discover the minimum plasma level or dose necessary for efficacy. Nevertheless, one can conclude that plasma levels of above 7 mg/l are robustly associated with response to carbamazepine, corresponding to daily doses of above 600 mg. For valproate, plasma levels above 50 mg/l appear to produce acceptable efficacy. These levels correspond to doses of 750 mg/day or (much) greater. It is interesting to note that, in the United States, where valproate (as divalproex) is licensed for the treatment of BAD, an initial dose of 750 mg/day is recommended, followed by titration to give a plasma level of between 50 and 125 mg/l. As if to confirm this, advertisements for divalproex state that 90% of patients in trials were treated with doses above 1000 mg/day.

These findings have important implications for prescribers. In the absence of data supporting the use of low doses or low plasma levels, the doses and plasma levels recommended here should be aimed for. This means that if our informal observations are a true reflection of prescribing practice, wholesale change in practice is called for.

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Table 1. Dose details in trials of carbamazepine/valproate in bipolar affective disorder

Study	n	Condition	Design	Outcome	Level details	Dose details
Carbamazepine						
Placidi *et al*, 1986	83	Prophylactic and acute treatment of BAD	Double-blind over 3 years	CBZ=Li	Target level was 7–12 mg/l	Not given
Lerer *et al*, 1987	34	Acute mania	Double-blind over 4 weeks	CBZ=Li	Target level was 8–12 mg/l	Median daily dose 1400 mg
Joyce, 1988	18	Rapid cycling	Open, over 6 months	7 showed improvement	Target level used but not stated	No summary details given
Lusznat *et al*, 1988	54	Prophylactic and acute treatment of BAD	Double-blind over up to one year	CBZ=Li	Responders mean levels=8 mg/l	Not given
Frankenburg, 1988	50 (34 BAD)	BAD	Retrospective over 3–4 years	Only 2 cases of good long term response	All pts had levels >8 mg/l	Not given
Okuma *et al*, 1990	105	Acute mania	Double-blind over 4 weeks	CBZ=Li	Mean level was 7.5 mg/l	Mean daily dose was 614 mg
Stuppaeck *et al*, 1990	24 (7 BAD)	Prophylaxis of 'mood disorders'	Open, naturalistic over mean of 20.2 mths	80% improved	Mean level was 5.7 mg/l	Daily doses generally 600/800 mg
Small *et al*, 1991	52	Mania	Double-blind over 8 weeks (2 yr follow up)	CBZ=Li	Mean level 8.7 mg/l at week 8	Mean daily dose 1036 mg at week 8
Valproate						
Brown, 1989	405	Manic depressive illness	Open, community-based	Response rate over 60% for BAD	Target level was 50–100 mg/l	Mean daily dose was 1200 mg
Calabrese *et al*, 1990	55	Rapid cycling	Open, naturalistic over 7.8 months	Marked acute/prophylactic response	Mean level was 84 mg/l	Mean dose was 1686 mg daily
Pope, 1991	36	Acute mania	Valproate vs placebo over 21 days	Valproate >> placebo	All levels in range–50–100 mg/l	All received at least 750 mg daily
Calabrese *et al*, 1992	78	Rapid cycling	Open, naturalistic over 15.8 months	Marked acute/prophylactic response	Mean level was 81 mg/l	Mean dose was 1498 mg daily
Jacobsen, 1993	33	Cyclothymia, bipolar II, mild rapid cycling	Open, naturalistic, over three years	79% reported sustained response	Mean level was 32.5 mg/l	Mean dose was 351 mg daily
Bowden *et al*, 1994	179	Acute mania	Divalproex vs lithium vs placebo – 21 days	Divalproex=lithium >> placebo	Mean on day 21=93 mg/l	Mean dose was 2000 mg daily (day 18)
Bowden *et al*, 1996	65	Acute mania	Relationship of plasma levels to efficacy/toxicity	Efficacy at >45 mg/l; toxicity at >125 mg/l	Mean on day 5 was 58.7 mg/l	All received 1000 mg daily by day 5

CBZ, Carbamazepine; Li, Lithium; a=b, efficacy not statistically different; a>>b, treatment a significantly more effective than b.

Recommendations

Carbamazepine – aim for plasma level >7 mg/l (>600 mg/day). Start at 200 mg BD; use modified release tablets; increase slowly.

Valproate – aim for plasma level of >50 mg/l (>750 mg/day). Start at 500 mg OD; use modified release tablets; increase slowly.

All samples for plasma levels should be taken immediately before the next scheduled dose.

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