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BIPOLAR DISORDERS

Brief Report

Carnitine does not improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted, low-fat diet

Elmslie JL, Porter RJ, Joyce PR, Hunt PJ, Mann JI. Carnitine does not improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted, low-fat diet.
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Objectives: Carnitine deficiency impairs fatty acid β-oxidation and may partly explain weight gain in valproate-treated patients. The aim of this study was to determine whether L-carnitine supplementation improves weight loss outcomes in bipolar patients taking sodium valproate.

Methods: Sixty bipolar patients with clinically significant weight gain thought to be related to sodium valproate, who had been taking sodium valproate for ≥6 months, were randomized to L-carnitine (15 mg/kg/day) or placebo for 26 weeks, in conjunction with a moderately energy-restricted, low-fat diet. The primary outcome measure was weight change.

Results: L-carnitine had no effect on mean weight loss compared with placebo (−1.9 kg versus − 0.9 kg) ($F = 0.778$, df = 1,58, $p = 0.381$). The number of people in each group able to lose any weight was identical ($\chi^2_1 = 0$, $p = 1.0$); more patients in the carnitine group (nine versus five) achieved a clinically significant weight loss (≥5%) but this was not statistically significant ($p = 1.0$, Fisher's exact test).

Conclusions: At the dose prescribed in this study carnitine supplementation did not improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted, low-fat diet.

Jane L Elmslie[a], Richard J Porter[a], Peter R Joyce[a], Penelope J Hunt[b] and Jim I Mann[c]

[a]Department of Psychological Medicine, [b]Department of Medicine, Christchurch School of Medicine and Health Sciences, [c]Department of Human Nutrition, University of Otago, Christchurch, New Zealand

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Corresponding author: Jane Elmslie, NZRD, PhD, Department of Psychological Medicine, Christchurch School of Medicine and Health Sciences, PO Box 4345, Christchurch, New Zealand.
Fax: +64 3372 0407; e-mail: jane.elmslie@chmeds.ac.nz

The specific determinants of weight gain in valproate-treated patients are unclear (1). Reliable data concerning its effect on energy balance are scarce (2), but increased appetite and thirst have been reported (1) and sedation and fatigue (3) may reduce physical activity levels. Therefore, interventions to reduce energy intakes and increase physical activity may be worthwhile.

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Impaired fatty acid β-oxidation is another possible contributor to chronic positive energy balance in patients taking valproate (2). Carnitine deficiency (plasma-free carnitine < 23 μmol/L), possibly due to increased urinary excretion, occurs in up to 80% of patients taking valproate (1, 4). Deficiency is most common in children, chronically ill patients, those taking more than one anticonvulsant and those with renal impairment (4, 5). Carnitine is necessary for the intracellular transport of long-chain fatty acids and when its availability is reduced β-oxidation is impaired, reducing the body's ability to use fat as an energy source (6). About 75% of the body's requirement for carnitine is met by diet, with the remainder being met by synthesis in the liver and kidneys (7). Endogenous synthesis requires

adequate intakes of a number of nutrients, including ascorbic acid; therefore carnitine status may be compromised by poor diet quality (6). Red meat and milk are the best dietary sources (6), but substantial increases in intakes of these foods may be impractical when energy intake restriction is required. Carnitine supplementation increases β-oxidation in both carnitine-deficient patients and healthy carnitine-sufficient volunteers (8, 9) and may enhance the effects of an energy-restricted, low-fat diet in valproate-treated patients.

The aim of this randomized, double-blind, placebo-controlled trial was to determine whether supplementation with L-carnitine improves weight loss outcomes in valproate-treated bipolar patients following an energy-restricted, low-fat diet.

Methods

Participants were recruited from among mental health services patients and by newspaper advertisement. Patients meeting DSM-IV criteria for bipolar disorder (BPD) types I or II, who had been taking sodium valproate for ≥ 6 months, with clinically significant weight gain that appeared to be related to valproate treatment, were eligible for the study. All participants had a body mass index (BMI) >25. Patients taking insulin, oral hypoglycaemic agents or antiobesity medication were excluded. The study was approved by the Canterbury Ethics Committee.

Participants were randomized using a computer-generated random number sequence to receive L-carnitine L-tartrate (Lonza, Basel, Switzerland) (15 mg/kg/day) (10) or placebo capsules daily for 26 weeks. Capsules were dispensed monthly by Christchurch Hospital Pharmacy. Investigators and participants were blind to the treatment condition. Diet plans were individualized, low-fat and moderately energy restricted (−500 kcal/day). All participants were encouraged to accumulate ≥ 30 min of regular physical activity (walking, swimming, jogging, biking) on ≥ 5 days each week. Lifestyle advice was reinforced fortnightly, at dietary counselling sessions with a registered dietitian (JLE).

The primary endpoint was change in weight measured fortnightly. Secondary outcome measures were change in BMI and waist circumference.

Plasma and urinary carnitine, plasma creatinine, ascorbic acid, valproate level and thyroid function were measured at weeks 0, 4 and 26. Participants also completed a diet record at these time-points.

At baseline all participants were assessed using the Structured Clinical Interview for DSM-IV (SCID 1) (11), Young Mania Rating Scale (YMRS) (12) and Montgomery–Asberg Depression Rating Scale (MADRS) (13). Mood was reassessed at weeks 13 and 26. Medication changes were recorded for all participants. Patients rated their dietary and supplement compliance out of 10 at the end of the study.

The study was powered to detect a difference in weight change of ≥ 3 kg between groups, based on a sample size of 25 subjects per group ($\alpha = 0.05$, $\beta = 0.20$) (14, 15). A further 10 subjects were recruited to allow for a dropout rate of one in five. The data were analysed using SPSS version 10 (SPSS Inc., Chicago, IL, USA). The primary analysis was a repeated measures analysis of variance (RM-ANOVA) using the last observation carried forward, with change in weight as the outcome measure, group (carnitine or placebo) as a between-subjects factor and time as a within-subjects factor. A secondary analysis was conducted using only data from patients who completed the study (n = 44).

RM-ANOVAs were also used for continuous secondary outcome measures. Univariate ANOVAs were performed with percentage weight loss as the dependent variable, group as a between-subjects factor and valproate or carnitine levels or treatment compliance as covariates.

The chi-squared test or, where the expected values were <5, Fisher's exact test were used to compare categorical variables between groups. Unpaired *t*-tests were used to compare continuous variables between groups at baseline. Results were considered significant at two-tailed $p < 0.05$.

Results

A total of 78 people were screened. Consent was obtained from 68 people. Eight did not begin treatment; two stopped valproate, three withdrew and three did not meet DSM-IV criteria for BPD. Sixty people were randomized (49 women and 11 men). Baseline characteristics are shown in Table 1.

Forty-four participants completed treatment with no significant difference between groups in dropout rate ($\chi^2_1 = 0.341$, $p = 0.559$).

The difference between groups in weight loss (kg) was not significant (time by group interaction $F = 0.778$, df = 1,58, $p = 0.381$) (Table 2). The number of people able to lose any weight in each group was identical ($\chi^2_1 = 0$, $p = 1.0$); more patients in the carnitine group (nine versus five) achieved a clinically significant weight loss (≥ 5%), but this was not statistically significant ($p = 1.0$, Fisher's exact test). The strength of these inferences remained unchanged when female data were

Table 1. Baseline characteristics of subjects (n = 60)

Variable	Carnitine	Placebo	p-value
Age	42 (10)	42 (13)	0.97
Sex (M/F)	6/24	5/25	1.0
Diagnosis (BPD I/II/NOS)	20/10/0	20/8/2	0.46
MADRS	12 (11)	6 (8)	0.012*
YMRS	3 (5)	2 (4)	0.238
Valproate dose (mg)	1577 (541)	1710 (848)	0.47
Time on valproate			0.454[a]
<6 months	2	4	
6–12 months	8	7	
1–5 years	17	12	
>5 years	2	6	
Weight gained on valproate (kg)	15.2 (9.9)	14.7 (13.7)	0.87
Valproate level (μmol/L)	500 (136)	438 (174)	0.132
Typical antipsychotic	1	2	1.0
Atypical antipsychotic	12	6	0.16
Clozapine/olanzapine	4	1	0.35
Lithium	2	5	0.42
SSRIs	17	16	1.0
Tricyclic	2	3	1.0
Baseline weight (kg)	94.7 (19.0)	94.1 (20.0)	0.91
Baseline BMI (kg/m^2)	33.4 (6.1)	33.8 (6.4)	0.78
Plasma creatinine (mmol/L)	0.06 (0.012)	0.09 (0.12)	0.230
Plasma-free carnitine (μmol/L)	27.9 (10.0)	28.3 (7.9)	0.86
Urine-free carnitine (μmol/L)	53.3 (45.6)	57.7 (58.2)	0.75

[a]The p value was calculated based on the four time points indicated.
BPD = bipolar disorder; NOS = not otherwise specified; MADRS = Montgomery–Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; SSRIs = selective serotonin reuptake inhibitors; BMI = body mass index.
*p < 0.05.

Table 2. Effect of carnitine supplementation on body weight, body mass index (BMI), waist circumference, plasma and urine-free carnitine

Variable	Carnitine (n = 30)	Placebo (n = 30)	p-value
Weight change (kg)	−1.9 (3.7)	− 0.9 (4.5)	0.381
Weight change (%)	−2.0 (4.2)	−0.9 (4.8)	0.387
BMI change (kg/m^2)	−0.6 (1.4)	−0.4 (1.6)	0.466
BMI change (%)	−2.0 (4.2)	−0.9 (4.8)	0.386
Waist circumference change (cm)	−3.9 (4.6)	−3.1 (7.0)	0.597
Plasma-free carnitine change (μmol/L)	9.4 (10.0)	0.83 (5.5)	<0.0001*
Urine-free carnitine change (μmol/L)	277.0 (256.0)	6.6 (77.3)	<0.0001*

*p < 0.05.

analysed separately. There was no significant effect of carnitine on BMI or waist circumference ($F = 0.539$, df = 1,58, $p = 0.466$ and $F = 0.283$, df = 1,58, $p = 0.597$, respectively). Amongst completers (n = 44), there was no significant effect of carnitine on weight loss (time by group $F = 0.965$, df = 1,42, $p = 0.331$).

Between group differences in energy intake were not significant (time by group interaction $F = 3.112$, df = 1,54, $p = 0.083$) but secondary ANOVA showed a main effect of self-perceived dietary compliance on percentage weight loss in the study population as a whole ($F = 29.742$, df = 1,51, $p < 0.0001$). Weight change was unaffected by baseline valproate or carnitine levels or supplement compliance and there was no interaction between these and group.

Plasma and urinary carnitine increased significantly over the 26 weeks in patients taking carnitine (Table 2). At baseline, 16 (27%) participants were carnitine-deficient as defined by plasma-free carnitine <23 μmol/L (4). The numbers of carnitine-deficient patients in each group were not significantly different ($\chi^2_1 = 1.193$, $p = 0.275$).

Significantly more patients in the carnitine group than the placebo group reported increases in weight-promoting medications (antipsychotics, mood stabilizers or tricyclic antidepressants) during the study [18.3% versus 5% ($\chi^2_1 = 5.963$, $p = 0.03$)].

Depression ratings (MADRS) were significantly different between groups at baseline (Table 1) but there was no group by time interaction ($F = 1.761$, df = 1,57, p = 0.190). Mania ratings were similar at baseline (Table 1) and there was no group by time interaction ($F = 2.167$, df = 1,57, p = 0.146).

Discussion

To our knowledge, this is the first study to evaluate the effectiveness of a dietary intervention for bipolar patients who have gained weight on sodium valproate. L-carnitine supplementation increased both plasma and urinary carnitine levels, but did not significantly improve weight loss outcomes. There was a statistically significant effect of dietary intervention on weight, BMI and waist circumference.

Carnitine supplementation has previously been shown to decrease respiratory quotient, a metabolic marker of β-oxidation (16), in carnitine-deficient epileptic children taking valproate (8) and, more recently, to increase the metabolism of fatty acids labelled with ^{13}C in healthy carnitine-sufficient subjects (9, 17). We hypothesized that carnitine would augment the effect of an energy-restricted, low-fat diet in our subjects by increasing fatty acid β-oxidation and that this would result in a significant difference in weight loss between groups.

The results were unexplained by differences in thyroid function, leucocyte ascorbate, plasma creatinine (data not shown) or dropout rates. However, there are several other possible explanations for our negative findings. The dose we used may have been too small. The amount of carnitine required to significantly affect the body pool is not well defined (18) and the doses reported to increase fatty acid oxidation in previous studies vary widely (8, 9, 17, 19). High doses are associated with unpleasant side effects, leading to high dropout rates (19, 20). For this reason we chose 15 mg/kg/day, an amount previously reported to reverse deficiency in carnitine-deficient children taking valproate (10). Because most of our subjects had normal carnitine status at baseline, this dose may have been insufficient. However, a significant increase in β-oxidation has been reported in healthy carnitine-sufficient subjects taking 10 mg/kg/day of L-carnitine L-tartrate (19) and the degree of change in plasma free and urinary carnitine we observed in the carnitine group was similar to that reported in healthy subjects taking twice the dose where an increase in fatty acid oxidation was measured directly (9).

Impaired β-oxidation is thought to develop in valproate-treated patients as a result of urinary excretion of valproyl carnitine (21), a by-product of the incomplete mitochondrial oxidation of valproate, but a number of observations support the view that other mechanisms may be responsible for this impairment. The kidney appears to conserve carnitine during valproate treatment (22), β-oxidation can be impaired in the face of normal carnitine status (23, 24) and, in a recent *in vitro* study, valproate was completely oxidized in mitochondria (25). A further study by the same authors reported that whereas valproyl carnitine levels were negligible in 18 adult patients on long-term valproate monotherapy, a significant increase in 3-hydroxy-isovaleryl carnitine suggested an effect on the mitochondrial respiratory chain via the enzymes involved in leucine metabolism (26). Under these circumstances carnitine supplementation would have little effect on β-oxidation. Our findings appear to be consistent with this hypothesis, bearing in mind that the results from small studies of patients on valproate monotherapy may not be generalizable to all patients taking valproate and those who gain weight on this medication may be a distinct subgroup.

A significant limitation of the present study is that, regardless of any increase in β-oxidation, weight loss could only occur in individuals in negative energy balance (whose intake was less than their expenditure). Therefore, only patients who complied sufficiently with the dietary aspects of the protocol could benefit from carnitine supplementation and this may be a small subgroup in clinical practice. In this regard, the significantly higher usage of weight-promoting medications during the study and higher MADRS scores at baseline in the carnitine group may have obscured a positive treatment effect of carnitine by increasing appetite and reducing physical activity.

In summary, at the dose prescribed in this study, carnitine supplementation made no difference to weight loss outcomes in bipolar patients taking sodium valproate. Although there was evidence that dietary intervention was beneficial, at least in some individuals, poor overall compliance with the dietary aspects of the protocol may have obscured any additional benefit of carnitine supplementation. Further research is required to determine effective means of weight reduction in overweight BPD patients taking sodium valproate.

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