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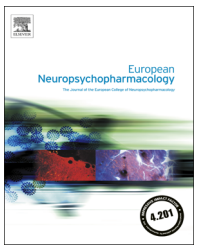

Sodium valproate in migraine without aura and medication overuse headache: A randomized controlled trial

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Abstract
Objective: To assess the efficacy, safety and tolerability of sodium valproate (800 mg/die) compared with placebo in medication-overuse headache patients with a history of migraine without aura.
Methods: This is a multicenter, randomized, double-blind, placebo-controlled study enrolled medication-overuse headache patients for a 3-month treatment period with sodium valproate (800 mg/day) or placebo after a 6 day outpatient detoxification regimen, followed by a 3-month follow-up. Primary outcome was defined by the proportion of patients achieving $\geq 50\%$ reduction in the number of days with headache per month (responders) from the baseline to the last 4 weeks of the 3-month treatment. Multivariate logistic regression models were used on the primary endpoint, adjusting for age, sex, disease duration, comorbidity and surgery. The last-observation-carried-forward method was used to adjust for missing values.
Results: Nine sites enrolled 130 patients and, after a 6-day detoxification phase, randomized 88 eligible patients. The 3-month responder rate was higher in the sodium valproate (45.0%) than in the placebo arm (23.8%) with an absolute difference of about 20% ($p=0.0431$). Sodium valproate had safety and tolerability profiles comparable to placebo.
Conclusions: The present study supports the efficacy and safety of sodium valproate in the treatment of medication overuse headache with history of migraine after detoxification.

1. Introduction

Medication-overuse headache (MOH) (Silberstein et al., 2008) is a chronic headache disorder having a relevant impact in clinical practice due to the long-term associated morbidity and disability (Grazzi et al., 2004; Kavuk et al., 2004). Few studies are available which specifically focus on the prophylactic treatment of patients affected by MOH (Zed et al., 1999; Paemeleire et al., 2006). Among the available drugs, sodium valproate (VPA) is a possible option. Clinical experience with this drug mainly concerns the management of primary headache forms. The drug has been approved by the FDA for migraine prevention. In a recent placebo-controlled study, VPA was used as prophylactic monotherapy of chronic daily headache and appeared superior to placebo in reducing pain frequency and intensity (Yurekli et al., 2008). VPA also appeared equally effective when compared to botulinum toxin A in reducing headache days, headache index and disability scores both in episodic and chronic migraine patients (Blumenfeld et al., 2008).

Psychiatric comorbidity in MOH is common and is considered as a risk factor for headache chronicity (Radat et al., 2005). VPA has also been demonstrated to be effective in bipolar disorders (Bowden and Singh, 2005). Thus, the drug could be helpful to both reverse the chronic pattern of headache in patients with MOH and improve psychiatric disturbances which often afflict these patients (Calabresi and Cupini, 2005).

The detoxification of the patients with MOH and the start of a prophylactic therapy is, nowadays, the standard of care worldwide (Olesen, 2012; Corbelli et al., 2012). The timing of prophylactic treatment after detoxification is one of the most debated aspect of MOH (Zeeberg et al., 2006), and is a matter of concerns among patients (Munksgaard et al., 2011). In a recent randomized open-label trial, a structured inpatient detoxification program, characterized by the prompt start of a preventive treatment, resulted more effective than advice alone or than a structured outpatient program in achieving withdrawal in patients with MOH (Rossi et al., 2013).

On this background, the Sodium vAlproate in the treatment of Medication Overuse HeadAche (SAMOHA) study group proposed a multicenter placebo-controlled study to verify the efficacy and tolerability of VPA in the short-term treatment of MOH after detoxification.

2. Experimental procedures

2.1. Standard protocol approvals, registrations, and patient consents

The Neurologic Clinic of Perugia (Italy) was the coordinating center and designed the study and the Mario Negri Institute for Pharmacological Research (Milan, Italy) was responsible for data collection, quality monitoring and statistical analysis. Safety management and central VPA titration was carried out by the Department of Neurosciences of the University of Messina (Italy). The planned duration of the study was 2 years. Before starting the study, the protocol was submitted for approval to the Ethics Committee of all participating centers. The trial has been registered on the European Union Drug Regulating Authorities Clinical Trials website (EudraCT code 2007-006773-92; https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-006773-92/IT). The study was conducted in accordance with the Declaration of Helsinki and its amendments (Seoul, October 2008), and with the CONSORT statement. All patients gave their consent to study participation.

2.2. Subjects

Consecutive outpatients attending to the participating centers, aged 18–65 years, with established past history of episodic migraine without aura, and a diagnosis of MOH according to the International Headache Society revised criteria (Silberstein et al., 2008) during the previous 3 months were eligible for inclusion. Furthermore, all other causes of secondary headache were ruled out. Patients had to be willing to comply with all appointments for clinic visits, tests, and with the procedures required by the protocol, and had to have

returned the informed consent form. Females were eligible only if of non-childbearing potential or using an adequate contraceptive method. Patients taking a headache-prevention medication during the month preceding enrollment were excluded, as were those affected by known allergic reactions to drugs or assuming prohibited concomitant therapy (other antiepileptic drugs; tricyclic antidepressants; anticoagulants; neuroleptics; abused benzodiazepines). Other exclusion criteria included history or suspicion of alcohol abuse or illicit drug use in the previous 2 years, past or present history of a serious illness, or metabolic disorder.

2.3. Treatment

This is a double-blind placebo-controlled study. Treatment included a 4-week baseline period (from Visit (V) 1, during which no study medication was given), followed by a 6-day inpatient detoxification phase (from V2 to V3, in which abused drugs were promptly discontinued) and a 12-week double-blind treatment period (from V3 to V8) with VPA 800 mg/day or placebo. After the detoxification phase, the patients were advised to discontinue the overused medication. Although acute medications were consented, no specific symptomatic drugs were recommended during follow-up. A follow-up visit (V9) at week 24 was made to verify the possibility of a carryover effect of VPA treatment. The choice of an 800 mg/day dosage was reached based on a compromise of the various dosages used in studies on headaches and in consideration of the potential side effects which could increase with an increased dose. At V3, eligible patients who completed the prospective baseline period and detoxification phase were sequentially assigned in a 1:1 ratio to either VPA or placebo and received a random computer-generated medication code number, in compliance with a permuted block randomization design. Neither the patients nor the clinic staff were aware of the study medication assigned. From V3 and throughout the entire follow-up, each patient received treatments bearing the same randomization code. During the titration period, each patient took 1 tablet in the first 2 days (at 8:00 p.m.), 2 tablets (1 at 8:00 a.m. and 1 at 8:00 p.m.) in days 3 and 4, 3 tablets in days 5 and 6, and 4 tablets per day thereafter (2 at 8:00 a.m. and 2 at 8:00 p.m.). Treatment was continued for a total of 12 weeks. In the last week of treatment the number of tablets was tapered down according to a scheme symmetrical to that of the titration period. VPA and placebo were indistinguishable, having the same appearance, smell, taste, and after-taste.

2.4. Primary outcome

The primary outcome was defined by the proportion of patients with $\geq$50% reduction in headache days per month (responder rate) from the prospective 4-week baseline phase to the last 4 weeks of the 3-month treatment.

2.5. Secondary outcomes

Secondary outcomes included (1) the number of days with headache and (2) headache intensity, measured with a 4-point scale with 0=no pain, 1=mild headache, 2=moderate headache, 3=severe headache; and changes in (3) the monthly frequency, duration and severity of headache attacks; (4) the number of days/month with acute medications; (5) MIgraine DisAbility queStionnaire (MIDAS) (Stewart et al., 2000); (6) Migraine Specific Quality of life questionnaire (MSQ) (Bagley et al., 2012); (7) Modified Mini-International Neuropsychiatric Interview (Modified-MINI) (Amorim et al., 1998); (8)-(9) Beck Anxiety Inventory (BAI) (Osman et al., 1997) and Beck Depression Inventory scales (BDI) (Richter et al., 1998); (10) Yale Brown Obsessive Compulsive Scale scores (YBOC) (Kim et al., 1990); (11) Leeds Dependence Questionnaire (LDQ) scores (Raistrick et al., 1994); (12) Satisfaction with Treatment Questionnaire (TSQM) (Atkinson et al., 2005); (13) Tolerability (number and type of adverse events; number and type of adverse events leading to treatment withdrawal).

Using a headache diary, patients recorded all headache attacks and drugs used during the study period at each visit. The safety and tolerability of VPA and placebo were also obtained from the patients diary. The effect of VPA and placebo on quality of life and psychopathological disturbances was tested at the end of the baseline period, (week -1), at the end of the treatment period (week $+12$), and at week $+24$: TSQM was also used at the end of the treatment period, at week $+12$ (or at the final visit in case of premature termination).

2.6. Follow-up

At V1,V2,V3,V5,V6,V8,V9, the patients underwent a physical examination.

Blood samples (for routine hematology, clinical chemistry and ammonia) were taken and urinalysis was carried out at the screening visit (week -5), randomization visit (week 0), and at weeks 4, 5, 6, 8 and 12. For females, urine human chorionic gonadotropin for pregnancy was tested at the same visits. Physical examination and interpretation of laboratory tests were performed by local physicians, who knew about the study design but did not belong to the investigators' group, to avoid compromising blinding. Investigators were promptly informed of the occurrence of exclusion criteria.

2.7. Statistical methods

From a review of the literature and the investigators' personal experience, the estimated proportion of patients with a spontaneous improvement in headache after detoxification was estimated at 29.5%. Estimating an increase of this percentage to 50% for patients assigned VPA, the enrollment of 70 patients in each therapeutic arm was needed, with a power (beta) of 80% and a level of statistical significance of 5% (1-tailed). Taking into account the drop-outs and the screening failures reported in previous studies (30%), the number of patients was increased to 200.

Descriptive statistics were reported as counts and percentages, mean and standard deviation (SD) or median and range. Categorical and continuous variables were compared between the two groups with the Fisher Exact test or the Chi Square test as appropriate and the Wilcoxon-Mann-Whitney Test. Changes in headache frequency, number of days with acute medications, and number of rescue drugs were compared using Analysis of Variance for repeated measures (ANOVArm). Correlations within patients were handled using the "unstructured" correlation matrix. The results of ANOVArm have been displayed as "treatment", "time" and "treatment $\times$ time" effects. The same analysis was used to compare YBOCS, LDQ, MSQ, Beck Depression and Anxiety Inventory scores calculated at the end of the baseline period, at the end of the treatment period, and after 3 months from discontinuation. Deltas of the value of each continuous outcome were assessed to compare the difference between the 12 and 24-week visit and the baseline assessment. Wilcoxon-Mann-Whitney and the signed-rank tests were used to assess differences between and within each group. Multivariable logistic regression models were applied on the primary endpoint to adjust for possible confounders or imbalances in the two groups (age, sex, disease duration, chronicity duration, co-morbidities and antecedent surgeries). Results are reported as ORs (odds ratios) and 95% confidence intervals (95% CIs). The Poisson distribution for count data was used to assess incidence and 95% CIs of adverse events in the two arms. Statistical analyses were performed in both the intent-to-treat (ITT) and completers populations. All efficacy outcomes in the ITT population were assessed using the last observation carry forward (LOCF) approach. Results reported in this work always refer to the ITT population unless

otherwise specified. All tests were two-tailed with significance set at alpha=0.05.

3. Results

Between April 2009 and June 2011 130 of the 200 planned patients were screened at the nine participating centers (from 13 to 18 patients per center). Recruitment was prematurely stopped because of a lack of eligible patients within the 2 years planned for the study. The principal cause of recruitment failure was the withdrawal of four centers, due to the delay in obtaining approval by the regional ethical committees.

Eighty-eight patients (from 8 to 11 per center) continued meeting the inclusion/exclusion criteria after the 4 baseline weeks and were then randomized to placebo or VPA (n=44 per arm). To avoid the possibility of missing an effect in one direction or another we opted to perform two-tailed tests and also due to the lack of patients, under the planned hypothesis, our study had 50% power to detect statistical significance. Figure 1 provides the disposition of study subjects. Fifteen patients withdrew (n=7 VPA and n=8 placebo) during the course of the trial. Patients taking VPA withdrew because of adverse events (n=3), low compliance (n=1), refusal to continue (n=1); and 2 additional patients were lost at follow-up. Patients taking placebo withdrew because of adverse events (n=2), lack of efficacy (n=2), unprotected sex (n=1); and 3 additional patients were lost at follow-up. Subject demographics and baseline medical and headache histories by treatment arm are summarized in Table 1.

3.1. Efficacy results

Responder rates at week 12 were higher in the VPA (45.0%) vs. the control arm (23.8%) with an absolute difference of about 20% (p=0.043). The LOCF imputation method uncovered 40 and 42 responders in the two arms (VPA and control). Allocating missing cases to failures, the proportion of successes changed to 18 (40.9%) and 10 (22.7%) (p=0.067). The multivariable logistic model reported a three-fold higher risk of failures in the control arm (p=0.039). Consistently with the responder rates, at week 12 the total number of headache days was significantly lower with VPA than with placebo. At the same point, 59.1% and 40.9% of patients respectively in VPA and control groups reverted to an episodic pattern of headache. These results were not maintained at week 24, 3 months after therapy discontinuation (Table 2). The mean (SD) baseline number of days with headache per month was similar in the two groups, respectively 21.8 (6.0) and 21.0 (4.6) in the control and VPA arms. The mean (SD) difference from baseline was significant at the 3-month visit, but not at the end of the study (p=0.012 and p=0.557). The ANOVArm model (comprising the last visit) reported a highly significant interaction with time (p=0.002) which confirmed differences in the "trajectories" of this endpoint in the two arms. The acute medication usage at week 12 was significantly reduced and the criteria for medication overuse were no longer present in 63.6% of patients treated with VPA and in 47.7% of patients in the control group. Headache was reported severe by 8 and 16 patients, 7 and 12 patients, 9 and 13 patients at baseline, week 12 and week 24 in the VPA and control arms respectively. No significant differences were detected.

Patients in both arms improved in all questionnaire scores. Patients treated with VPA reported a significantly higher improvement at the 12 weeks visit in the MSQ and Y-BOCS scores (p=0.002 and p=0.042) and a borderline improvement in the MIDAS, Beck anxiety and Beck depression scores (p=0.074, p=0.060, p=0.079). At the 24 week visit differences were non-significant. The MSQ was the only questionnaire to point out a significant "time × group" interaction in the ANOVArm model (p=0.003). The TSQM scores were similar in the two treatment arms in the total

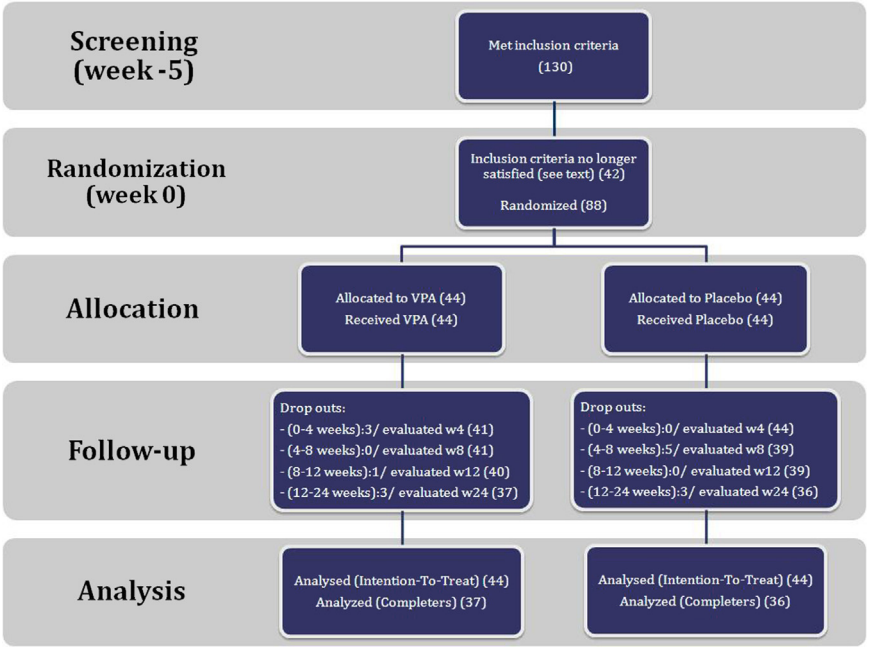

Figure 1 Subjects eligibility and follow-up.

Table 1 Demographical and clinical characteristics of the sample.

		VPA *n* (%)	Placebo *n* (%)
Sex	*Female*	34 (77.3)	35 (79.5)
	Male	10 (22.7)	9 (20.5)
Age class (years)	*18-34*	8 (18.2)	5 (11.4)
	35-44	14 (31.8)	20 (45.5)
	45-54	17 (38.6)	13 (29.5)
	55-64	5 (11.4)	6 (13.6)
BMI class	*Underweight* <18	27 (62.8)	24 (54.5)
	Normal weight 18-24.9	9 (20.9)	14 (31.8)
	Overweight 25-29.9	2 (4.7)	1 (2.3)
	Obese ≥ 30	5 (11.6)	5 (11.4)
	No	1	-
Comorbidity	*No*	37 (84.1)	29 (65.9)
	Yes	7 (15.9)	15 (34.1)
Surgery	*No*	10 (22.7)	18 (40.9)
	Yes	34 (77.3)	26 (59.1)
Headache duration	<10 *y*	6 (13.6)	7 (15.9)
	11-20 y	13 (29.5)	7 (15.9)
	21-30 y	13 (29.5)	16 (36.4)
	>30 *y*	12 (27.3)	14 (31.8)
MOH duration	<1 *y*	6 (13.6)	6 (13.6)
	1-3 y	10 (22.7)	15 (34.1)
	3-5 y	12 (27.3)	8 (18.2)
	>5 *y*	16 (36.4)	15 (34.1)
Overused drugs	*Analgesics* >14 *d*	15 (34.1)	15 (34.1)
	Analgesic combinations >9 *d*	5 (11.4)	7 (15.9)
	Drug combinations >9 *d*	9 (20.5)	13 (29.5)
	Triptan combinations >9 *d*	15 (34.1)	9 (20.5)

BMI=Body mass index.

Table 2 Efficacy results (headache characteristics).

	Responder rate	***VPA***	***Placebo***	***p-value***	***OR (95% CI)***	***Adj. OR (95% CI)***
Week 12	*N*(%)	$18(45.0)_{;4}$	$10(23.8)_{;2}$	0.043	2.6 (1.0-6.7)	3.4 (1.1-11.1)
Week 24	*N*(%)	$14(35.0)_{;4}$	$17(40.5)_{;2}$	0.609	0.8 (0.3-1.9)	0.7 (0.3-2.0)
	Change in the # of days with headache/month	***VPA***	***Placebo***	***p-value***	***p-"time"***	***p-"time × group"***
Week 12	Δ Mean (SD)	−8.1 (6.7)	−4.6 (6.8)	0.012	<0.0001	0.094
Week 24	Δ Mean (SD)	−5.3 (7.9)	−6.5 (6.8)	0.557	<0.0001	0.002
	Change in the # of days with acute medications	***VPA***	***Placebo***	***p-value***	***p-"time"***	***p-"time × group"***
Week 12	Δ Mean (SD)	−8.6 (6.8)	−4.9 (8.8)	0.013	<0.0001	0.149
Week 24	Δ Mean (SD)	−5.2 (8.7)	−6.5 (8.2)	0.822	<0.0001	0.003
	Change in severity of headache (improvement)	***VPA***	***Placebo***	***p-value***		
Week 12	*N*(%)	$8(18.2)_{;-}$	$8(18.2)_{;-}$	1.000		
Week 24	*N*(%)	$5(11.4)_{;-}$	$8(18.2)_{;-}$	0.367		

Data referred to the ITT population. Missing data with at least one assessment were handled with the LOCF imputation method.
The number of missing data without any assessment are displayed as subscript "*n*".
Responder rate was defined by the proportion of patients having a $\geq 50\%$ reduction of headache days per month.
OR=Odds ratio; Adj OR=Adjusted the odds ratio; CI=Confidence interval; SD=Standard deviation.
"time"=Effect of time (ANOVArm); "time × group"=Interaction between treatment arm and time (ANOVArm).

Table 3 Efficacy results (functional disability, quality of life and psychopathological features).

		VPA	*Placebo*	*p-value*	*p-"time"*	*p-"time × group"*
MIDAS						
Week 12	Δ Mean (SD)	−35.6 (54.4)	−17.4 (39.7)	0.074	<0.0001	0.180
Week 24	Δ Mean (SD)	−31.7 (54.5)	−15.5 (38.3)	0.080		
MSQ						
Week 12	Δ Mean (SD)	−15.4 (14.5)	−6.1 (11.3)	0.002	<0.0001	0.003
Week 24	Δ Mean (SD)	−11.6 (13.3)	−7.8 (12.1)	0.330		
Leed dependency						
Week 12	Δ Mean (SD)	−4.5 (5.9)	−2.6 (4.0)	0.122	<0.0001	0.210
Week 24	Δ Mean (SD)	−4.2 (5.9)	−2.7 (4.3)	0.166		
Y-BOCS						
Week 12	Δ Mean (SD)	−1.6 (4.4)	−0.1 (1.6)	0.042	0.027	0.096
Week 24	Δ Mean (SD)	−1.5 (4.6)	−0.4 (1.7)	0.642		
Beck anxiety						
Week 12	Δ Mean (SD)	−3.7 (5.6)	−1.6 (5.5)	0.060	<0.0001	0.150
Week 24	Δ Mean (SD)	−3.3 (6.5)	−1.2 (4.8)	0.134		
Beck depression						
Week 12	Δ Mean (SD)	−4.2 (6.2)	−1.5 (3.4)	0.079	<0.0001	0.052
Week 24	Δ Mean (SD)	−4.1 (7.0)	−1.9 (3.8)	0.354		
TSQM (total)						
Week 12	Mean (SD)	271.6 (78.8)	260.9 (52.3)	0.411	-	-

Data referred to the ITT population. Missing data with at least one assessment were handled with the LOCF imputation method.
SD=Standard deviation.
p-time=Effect of time (ANOVArm); "time × group"=Interaction between treatment arm and time (ANOVArm).

scale (Table 3) and in its subscales (data not shown). According to the MINI International Neuropsychiatric Interview, at the baseline visit there was a cumulative number of disorders equal to 36 and 37 in the VPA and control arms respectively. Twelve weeks later the count decreased to 24 and 26. At the end of the follow-up the disorders were 26 and 20.

3.2. Safety results

The number of adverse events (95% CI) registered in the VPA and the control arms during the course of the trial was 37 (26.1–51.0) and 45 (32.8–60.2) (p=0.3766) respectively. Many of them were the recurrence of the same event. All adverse events are reported in Table 4. There were no deaths. Adherence to treatment did not differ between the VPA and the control group (data not shown).

Table 4 Adverse events reported in VPA and placebo arm.

	VPA *n*	Placebo *n*
Decline in sexual desire	0	1
Depression	0	1
Nausea/vomiting	3	1
Sleepiness	1	0
Worsening headache	1	1
Heartburn	0	1
Diarrhea	1	2
Asthenia/fatigue	0	1
Weight gain	1	2
Hair loss	5	1
Tremor	1	0
Pruritus	2	1
Flu like syndrome	4	6
Cystitis	1	0
Dizziness	0	1
Back pain	2	3
Neck pain	2	1
Pre-syncope	1	2

4. Discussion

This is the first randomized trial investigating the efficacy of VPA in the prophylactic treatment of MOH after detoxification. In our study, most efficacy outcomes reported a significant superiority or a trend toward a superiority of VPA over placebo. In particular, a greater responder rate after 3 months of treatment was found in the VPA group compared to the control group (45% vs. 23%). Furthermore, a statistically significant decrease in the headache days per month when comparing VPA to placebo in the ITT population was found at the end of the 3rd month of treatment, with rates of 59.1% and 40.9% of patients reverting to an episodic pattern (<15 days/month with headache). A significant

reduction in the acute medication usage from baseline was also observed and 63.6% of patients treated with VPA did not fulfill the criteria for medication overuse compared to 47.7% of patients in the control group. The efficacy of VPA was also suggested by a borderline improvement of quality of life and migraine disability. These results cannot be explained only by the detoxification regimen (the same in both treatment arms). In this daily dose, the drug appears well-tolerated due to the equal number of patients reporting adverse events in the VPA and control arms and the fairly low number of reports and discontinuations for poor tolerability. The number and type of adverse events observed confirm the safety of VPA at the dosage of 800 mg/day also considering the potential risk of handling VPA in young fertile women. This study was designed in agreement with the recent EFNS guidelines for the treatment of MOH (Evers and Jensen, 2011).

Our study confirms previous observations about the occurrence of psychopathological disturbances in chronic headache patients with MOH (Radat et al., 2005; Atasoy et al., 2005; Sances et al., 2010; Galli et al., 2011). However, we did not find that VPA had a significant effect on psychopathological comorbidity, suggesting that its anti-migraine action is independent from its potential impact on the underlying psychopathology. Recent findings from biochemical and neuropharmacological research about novel and dose-related mechanisms of action of VPA, as well as observations on the pharmacogenomic profiles of patients, could in part explain this dichotomy, which needs to be further investigated (Xu et al., 2007; Rosenberg, 2007; D'Souza et al., 2009; Terbach and Williams, 2009). However, in light of the small sample, the study may not be powered to detect minor differences.

The fairly high proportion of responders in the control arm can be explained by drug withdrawal and the placebo effects. Their trend is in line with that reported in previous studies involving prophylactic treatment of episodic and chronic headache with oral medications (Autret et al., 2012; Rossi et al., 2013). The significant reduction in headache days, together with the decrease in the number of acute medications used to antagonize headache, supports a specific biological effect of VPA in the preventive treatment of MOH, as previously shown for episodic and chronic migraine patients. MOH is a very heterogeneous disorder and it is not possible to propose a single adequate management. It can be argued that our patients, enrolled by third-level headache centers, are more difficult to be treated and, therefore, could need a prompt preventive treatment after detoxification. It may not be the same for patients with lower medical needs managed by family physicians. These latter patients could benefit from simple advice alone.

In our study VPA does seem to have a short term carry-over effect as shown by the reversal to the baseline headache patterns (38.2% and 41.4% in the VPA and control arms respectively) and by the daily intake of symptomatic drugs in the two groups (non-abuse pattern rates in the VPA and control arms were 50.0% and 47.7% respectively) at the end of the follow-up (24th week). This finding is in contrast with results of a previous open label study reporting a positive response in a series of patients with transformed migraine treated with VPA for a period not exceeding 12 weeks which was maintained for at least 2 months after discontinuation (Rothrock and Mendizabal, 2000). This suggests that a 3 months period of treatment may not be enough to antagonize central sensitization caused by repeated headache attacks reinforced by the overuse of acute medication. A long-term treatment with VPA should therefore be considered to maintain a positive effect on headache and drug overuse considering the higher rate of relapses after 1 year after detoxification observed in previous studies (Rossi et al., 2008; Hagen et al., 2010; Hagen et al., 2011).

A number of important limitations need to be considered. Firstly the required sample size was not met perhaps due to our strict eligibility criteria and the high number of screening failures. However, despite the small sample size, the higher than expected difference in efficacy between VPA and placebo at 12-week treatment attained statistical significance and was consistently accompanied by improvement in a number of secondary outcomes. Secondly, the use of the LOCF method to adjust for missing values and drop-outs can be contended. Since this method strongly assumes that the value of the outcome remains unchanged after a patient's drop-out, this may not be the case for several patients who decided to withdraw. However, data dragging underestimates treatment effect, resulting in a more conservative approach and may also cause a reduction of the variance, increasing the power of the statistical tests. In addition, the results remained substantially unchanged when considering all drop-outs treatment failures. Thirdly, only the patients with a previous history of migraine, but not of tension-type headache, were enrolled in the study. Patients with tension-type headache were purposedly excluded because VPA is apparently less effective in these patients than in those with a history of migraine (Freitag et al., 2001; Linde et al., 2013). Finally, only the 800 mg daily dose given for 3 months was tested and we do not know whether longer periods of treatment could be more effective.

In conclusion, the results of our study can confidently confirm the efficacy, after detoxification, of a short-term treatment with VPA given at 800 mg/day in reducing the number of days with headache and improving quality of life and disability in patients with MOH with a history of migraine. However, the effect of treatment is transient suggesting that higher daily doses and/or longer treatment periods may be required. The tolerability and the risk:benefit ratio of these treatment schedules should be assessed in future trials. Moreover, both primary care physicians and neurologists treating with VPA women in childbearing age should be aware about the risk of possible teratogenic effects of this drug and, for this reason, they should strongly advice effective birth control while taking the drug.

Conflict of interest statement

Dr. Sarchielli, Dr. Messina, Dr. Cupini, Prof. Tedeschi, Prof. Di Piero, Prof. Livrea, Prof. Pini, Prof. Bernardi, Prof. Bono, Prof. Sandrini, Dr. Caproni, Dr. Corbelli, Prof. Pisani, Prof. Beghi report no disclosures; Prof. Calabresi received research grants from Bayer, Schering, Biogen, Boehringer Ingelheim, Eisai, Novartis, Lundbeck, Merck Sharp & Dohme, Sanofi-Aventis, Sigma-Tau, and UCB Pharma.

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Dr. Sarchielli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Dr. Messina contributed in drafting/revising the manuscript, analysis and interpretation of data and statistical analysis.

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References

Amorim, P., Lecrubier, Y., Weiller, E., Hergueta, T., Sheehan, D., 1998. DSM-IH-R psychotic disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. Eur. Psychiatry 13, 26–34.

Atasoy, H.T., Atasoy, N., Unal, A.E., Emre, U., Sumer, M., 2005. Psychiatric comorbidity in medication overuse headache patients with pre-existing headache type of episodic tension-type headache. Eur. J. Pain 9, 285–291.

Atkinson, M.J., Kumar, R., Cappelleri, J.C., Hass, S.L., 2005. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health 8 (Suppl. 1), S9–S24.

Autret, A., Valade, D., Debiais, S., 2012. Placebo and other psychological interactions in headache treatment. J. Headache Pain 13, 191–198.

Bagley, C.L., Rendas-Baum, R., Maglinte, G.A., Yang, M., Varon, S.F., Lee, J., Kosinski, M., 2012. Validating migraine-specific quality of life questionnaire v2.1 in episodic and chronic migraine. Headache 52, 409–421.

Blumenfeld, A.M., Schim, J.D., Chippendale, T.J., 2008. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache 48, 210–220.

Bowden, C.L., Singh, V., 2005. Valproate in bipolar disorder: 2000 onwards. Acta Psychiatr. Scand. (Suppl. 426), S13–S20.

Calabresi, P., Cupini, L.M., 2005. Medication-overuse headache: similarities with drug addiction. Trends Pharmacol. Sci. 26, 62–68.

Corbelli, I., Caproni, S., Eusebi, P., Sarchielli, P., 2012. Drug-dependence behaviour and outcome of medication-overuse headache after treatment. J. Headache Pain 13, 653–660.

D'Souza, A., Onem, E., Patel, P., La Gamma, E.F., Nankova, B.B., 2009. Valproic acid regulates catecholaminergic pathways by concentration-dependent threshold effects on TH mRNA synthesis and degradation. Brain Res. 1247, 1–10.

Evers, S., Jensen, R., European Federation of Neurological Societies, 2011. Treatment of medication overuse headache – guideline of the EFNS headache panel. Eur. J. Neurol. 18, 1115–1121.

Freitag, F.G., Diamond, S., Diamond, M.L., Urban, G.J., 2001. Divalproex in the long-term treatment of chronic daily headache. Headache 41, 271–278.

Galli, F., Pozzi, G., Frustaci, A., Allena, M., Anastasi, S., Chirumbolo, A., Ghiotto, N., Guidetti, V., Matarrese, A., Nappi, G., Pazzi, S., Quartesan, R., Sances, G., Tassorelli, C., 2011. Differences in the personality profile of medication-overuse headache sufferers and drug addict patients: a comparative study using MMPI-2. Headache 51, 1212–1227.

Grazzi, L., Andrasik, F., D'Amico, D., Usai, S., Kass, S., Bussone, G., 2004. Disability in chronic migraine patients with medication overuse: treatment effects at 1-year follow-up. Headache 44, 678–683.

Hagen, K., Albretsen, C., Vilming, S.T., Salvesen, R., Grønning, M., Helde, G., Gravdahl, G., Zwart, J.A., Stovner, L.J., 2011. A 4-year follow-up of patients with medication-overuse headache previously included in a randomized multicentre study. J. Headache Pain 12, 315–322.

Hagen, K., Jensen, R., Bøe, M.G., Stovner, L.J., 2010. Medication overuse headache: a critical review of end points in recent follow-up studies. J. Headache Pain 11, 373–377.

Kavuk, I., Katsarava, Z., Selekler, M., Sayar, K., Agelink, M.W., Limmroth, V., Diener, H.C., 2004. Clinical features and therapy of medication overuse headache. Eur. J. Med. Res. 9, 565–569.

Kim, S.W., Dysken, M.W., Kuskowski, M., 1990. The Yale-Brown obsessive-compulsive scale: a reliability and validity study. Psychiatry Res. 34, 99–106.

Linde, M., Mulleners, W.M., Chronicle, E.P., McCrory, D.C., 2013. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database Syst. Rev. 6, CD010611.

Munksgaard, S.B., Allena, M., Tassorelli, C., Rossi, P., Katsarava, Z., Bendtsen, L., Nappi, G., Jensen, R., Comoestas Consortium, 2011. What do the patients with medication overuse headache expect from treatment and what are the preferred sources of information? J. Headache Pain 12, 91–96.

Olesen, J., 2012. Detoxification for medication overuse headache is the primary task. Cephalalgia 32, 420–422.

Osman, A., Kopper, B.A., Barrios, F.X., Osman, J.R., Wade, T., 1997. The Beck anxiety inventory: reexamination of factor structure and psychometric properties. J. Clin. Psychol. 53, 7–14.

Paemeleire, K., Crevits, L., Goadsby, P.J., Kaube, H., 2006. Practical management of medication-overuse headache. Acta Neurol. Belg. 106, 43–51.

Radat, F., Creac'h, C., Swendsen, J.D., Lafittau, M., Irachabal, S., Dousset, V., Henry, P., 2005. Psychiatric comorbidity in the evolution from migraine to medication overuse headache. Cephalalgia 25, 519–522.

Raistrick, D., Bradshaw, J., Tober, G., Weiner, J., Allison, J., Healey, C., 1994. Development of the Leeds dependence questionnaire (LDQ): a questionnaire to measure alcohol and opiate dependence in the context of a treatment evaluation package. Addiction 89, 563–572.

Richter, P., Werner, J., Heerlein, A., Kraus, A., Sauer, H., 1998. On the validity of the Beck depression inventory: a review. Psychopathology 31, 160–168.

Rosenberg, G., 2007. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? Cell Mol. Life Sci. 64, 2090–2103.

Rossi, P., Faroni, J.V., Nappi, G., 2008. Medication overuse headache: predictors and rates of relapse in migraine patients with low medical needs. A 1-year prospective study. Cephalalgia 28, 1196–1200.

Rossi, P., Faroni, J.V., Tassorelli, C., Nappi, G., 2013. Advice alone versus structured detoxification programmes for complicated medication overuse headache (MOH): a prospective, randomized, open-label trial. J. Headache Pain 14, 10.

Rothrock, J.F., Mendizabal, J.E., 2000. An analysis of the "carry-over effect" following successful short-term treatment of transformed migraine with divalproex sodium. Headache 40, 17–19.

Sances, G., Galli, F., Anastasi, S., Ghiotto, N., De Giorgio, G., Guidetti, V., Firenze, C., Pazzi, S., Quartesan, R., Gallucci, M., Nappi, G., 2010. Medication-overuse headache and personality: a controlled study by means of the MMPI-2. Headache 50, 198–209.

Silberstein, S., Tfelt-Hansen, P., Dodick, D.W., Limmroth, V., Lipton, R.B., Pascual, J., Wang, S.J., Task Force of the International Headache Society Clinical Trials Subcommittee, 2008. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia 28, 484–495.

Stewart, W.F., Lipton, R.B., Kolodner, K.B., Sawyer, J., Lee, C., Liberman, J.N., 2000. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain 88, 41–52.

Terbach, N., Williams, R.S., 2009. Structure–function studies for the panacea, valproic acid. Biochem. Soc. Trans. 37, 1126–1132.

Xu, X., Müller-Taubenberger, A., Adley, K.E., Pawolleck, N., Lee, V. W., Wiedemann, C., Sihra, T.S., Maniak, M., Jin, T., Williams, R. S., 2007. Attenuation of phospholipid signaling provides a novel mechanism for the action of valproic acid. Eukaryot. Cell 6, 899–906.

Yurekli, V.A., Akhan, G., Kutluhan, S., Uzar, E., Koyuncuoglu, H.R., Gultekin, F., 2008. The effect of sodium valproate on chronic daily headache and its subgroups. J. Headache Pain 9, 37–41.

Zed, P.J., Loewen, P.S., Robinson, G., 1999. Medication-induced headache: overview and systematic review of therapeutic approaches. Ann. Pharmacother. 33, 61–72.

Zeeberg, P., Olesen, J., Jensen, R., 2006. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. Cephalalgia 26, 1192–1198.