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High-dose versus low-dose valproate for the treatment of juvenile myoclonic epilepsy: Going from low to high

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Abstract

Juvenile myoclonic epilepsy (JME) is a genetic generalized epilepsy accounting for 3–12% of adult cases of epilepsy. Valproate has proven to be the first-choice drug in JME for controlling the most common seizure types: myoclonic, absence, and generalized tonic-clonic (GTC). In this retrospective study, we analyzed seizure outcome in patients with JME using valproate monotherapy for a minimum period of one year. Low valproate dose was considered to be 1000 mg/day or lower, while serum levels were considered to be low if they were at or below 50 mcg/dl. One hundred three patients met the inclusion criteria. Fifty-six patients (54.4%) were female. The current average age was 28.4 ± 7.4 years, while the age of epilepsy onset was 13.6 ± 2.9 years. Most patients corresponded to the subsyndrome of classic JME. Forty-six (44.7%) patients were free from all seizure types, and 76 (73.7%) patients were free from GTC seizures. No significant difference was found in seizure freedom among patients using a low dose of valproate versus a high dose ($p=0.535$), or among patients with low blood levels versus high blood levels ($p=0.69$). In patients with JME, it seems appropriate to use low doses of valproate (500 mg to 1,000 mg) for initial treatment and to evaluate to determine if freedom from seizures was attained.

Keywords

Blood Level; Valproate; Juvenile Myoclonic Epilepsy; Antiepileptic drugs; Epilepsy/Seizures; Dose

1. Introduction

Juvenile myoclonic epilepsy (JME), previously called idiopathic generalized epilepsy, is a genetic generalized epilepsy (GGE), currently classified by the International League Against Epilepsy (ILAE) as an electroclinical syndrome.¹ JME appears around puberty and is characterized by seizures with bilateral, single, or repetitive arrhythmic, irregular myoclonic jerks, predominantly in the arms, without disturbance of consciousness. Often there are generalized tonic-clonic seizures and, less often, infrequent absences. JME is a very common, if not the most common, form of GGE, accounting for 3% (population-based prevalence) to 12% (clinic- and hospital-based prevalence) of cases.²⁻³

In the original cohort of 47 patients studied by Janz and Christian, treatment with barbiturates controlled satisfactory “petit mal and grand mal seizures.”⁴ Barbiturates were the treatment of choice until 1984, when valproate (VPA) was reported for the first time to have remarkable potency in JME.^{5,6} Other drugs presently considered suitable for treatment of JME are clonazepam⁷, lamotrigine (LTG)⁸⁻¹⁰, levetiracetam (LEV)¹¹, topiramate¹²⁻¹⁴, phenobarbital (PB), valproate (VPA), and zonisamide (ZNS).¹⁵ Lacosamide (LCS) has not shown effectiveness in JME.¹⁶

Over the years, VPA has proven to be the first-choice drug for JME, with restrictions in women of childbearing age. A prospective randomized trial in patients with GGE showed more effectiveness and better tolerance with VPA compared to LTG and TPM.¹⁷⁻²⁰

Despite VPA's acceptance as the first-line treatment for JME, the most appropriate VPA dose in patients with JME has not yet been established. A satisfactory response to a low dose of VPA (400–500 mg per day) can occur, achieving complete freedom from GTC and absence of seizures, but incomplete control of myoclonic seizures.²¹⁻²² No significant differences in seizure frequency were observed when a daily dose of 1,000 mg of VPA was compared to a daily dose of 2,000 mg²³⁻²⁴; furthermore, increasing doses of VPA until side effects appeared did not appear to be very efficient.²⁵

The question that inspired our research was: what would be the appropriate dose and/or blood levels for VPA therapy in patients with JME? In an effort to answer this question, we compared seizure freedom between patients with JME taking a low dose of VPA with patients with JME taking a high dose of VPA. We also compared seizure freedom in patients with low VPA blood levels versus patients with high VPA blood levels.

2. Methods

2.1. Subject selection

We obtained clinical data from medical records of patients with JME who had been admitted to the epilepsy and genetic clinics of the National Institute of Neurology and Neurosurgery “MVS” from 2009 to 2012. Selected patients had to be taking VPA monotherapy for a minimum period of one year. The study was approved by the Institute's Research and Ethics Committees.

2.2. Data collection

Diagnosis of JME was performed using the criteria established by the International Genetic Epilepsy Studies Consortium (GENESS) following the ILAE 1989 commission.²⁶ We included medical records that had the following variables: VPA dose, blood levels, and length of time taking VPA; if any of these variables were missing, records were excluded. The last taken dose of VPA was recorded, and the patient must have been on that dose for at least one year of monitoring. The dose was classified as either low (<1000 mg) or high (>1000 mg) for analysis. VPA blood levels corresponded to the levels achieved with the last dose of VPA recorded in the patient's medical records. VPA blood levels were then divided into 50 mcg/dl and > 50 mcg/dl for analysis.

Other clinical variables were also documented, such as: current age, age at epilepsy onset, weight, gender, seizure types (isolated presence of myoclonias or their presence in combination with GTC, absence, and astatic seizures), JME subsyndrome, seizure freedom or poor control, electroencephalogram (EEG) findings, queries about family history of epilepsy, perinatal history, history of febrile seizures, history of moderate to severe head trauma, history of psychiatric disease prior to onset of epilepsy, previously used antiepileptic drugs (AEDs), relapses due to poor compliance, trigger factors, neuroimaging studies such as brain computed tomography (CT) or magnetic resonance imaging (MRI), presence of thyroid disease, and use of antidepressants.

Family history of epilepsy was documented in first-, second-, or third-degree relatives. Abnormal history of perinatal disorders was considered present when data included problems in pregnancy, fetal distress, neonatal hypoxia, or jaundice. Febrile seizures were considered present when seizures associated with hyperthermia occurred between 6 months and 6 years of age.

EEG records were classified as: 1. normal: normal background, without epileptiform activity, asymmetries, or dysfunction; 2. abnormal typical: generalized and bilateral symmetrical and synchronous polyspike 4 to 6 Hz polyspike wave complexes, and/or 3 to 4 Hz spike and slow wave complexes; 3. abnormal atypical: EEG with focal discharges (spikes or sharp waves), asymmetries, and focal or generalized dysfunction as described by Betting et al.²⁷ For analysis purposes, both typical and atypical findings were considered to be abnormal. The subsyndromes of JME were classified as previously described by Martínez-Juárez et al.²⁸

“Persistent seizures” were defined as the presence of any seizure type (including absences, myoclonias, astatic and/or GTC) in the last year, whereas “seizure-free” was defined as a lack of any seizure types for one year according to the ILAE criteria for seizure freedom.²⁹ AED intake prior to the use of VPA was recorded; the previous use of benzodiazepines, LTG, PB, LEV, and TPM were considered appropriate. However, the previous use of phenytoin (PHT) or carbamazepine (CBZ) was considered to be inappropriate. Relapses from poor adherence were recorded. Triggers were also obtained for the purpose of documenting seizure relapses associated with sleep deprivation, stress, fatigue, alcohol, menstruation, photic stimulation, and fasting.

Because this was a retrospective study, some clinical data were missing from patients' records; missing or unknown data are described in the tables, but were excluded when comparison analysis was performed.

2.3. Statistical analysis

The data were entered into a database for analysis. All calculations were performed with SPSSv17. Descriptive statistics used percentages and means for categorical and numeric variables, respectively. Comparisons between groups were performed using univariate analysis; a chi-square or Fisher's exact test were used for nominal variables, while Student's *t*-test or the Mann-Whitney U test were used for numeric variables.

3. Results

We reviewed 201 medical records of patients diagnosed with JME; 103 patients were on VPA monotherapy with at least one year of follow-up. Patients' seizure frequency was recorded together with VPA daily doses and VPA blood levels. We excluded 98 patients: six were on another monotherapy; 31 had incomplete data; 36 were on polytherapy with VPA; and 25 did not meet the criteria for JME, as they had other GGE.

3.1. Clinical characteristics

Among the patients, 56 (54.4%) were female, with an average current age of 28.4 ± 7.4 years (range 16–50). The mean age of epilepsy onset was 13.6 ± 2.9 years (range 6–23). Eighty-six patients (83.4%) belonged to the subsyndrome of classical JME. Ten (9.7%) patients had JME with astatic seizures, while seven (6.7%) patients had childhood absence that evolved to JME during adolescence.

The average time of use of VPA was 7.7 ± 6.6 years (range 1–30). VPA was the first drug used in 40 patients (40.8%), the second drug in 34 patients (33%), the third in 17 (16.5%), the fourth in nine (8.7%), and the sixth drug in one (1%). Sixty patients (58.3%) had used an AED that aggravated seizures in JME before taking VPA. Twenty-two (21.35%) patients had a history of perinatal complications, while 77 (79.3%) patients denied any history of perinatal complications and four (4.1%) patients said they did not know. Four (3.9%) patients had a history of febrile seizures during infancy and childhood, while 86 (88.58%) patients denied it and 13 (13.3%) ignored the history of febrile seizures. Family history of epilepsy was present in 56 (54.4%) patients. Of these 56 patients, 31 (30.1%) had a first-degree relative with a history of epilepsy, 16 (15.5%) had a second-degree relative, and nine (8.7%) a third-degree relative with a history of epilepsy.

All patients had interictal EEGs. Fifty-five (53.4%) patients had a normal EEG, while 48 (46.6%) had an abnormal EEG and 23 (22.3%) had abnormal typical EEGs. Twenty-five (24.5%) patients had abnormal atypical EEGs. Among the 103 patients, only 92 (94.8%) had a neuroimaging study performed (either CT or MRI), with normal results occurring in 49 (53.2%) patients.

Thyroid disease was found in nine (8.7%) patients; eight of these had hypothyroidism. Depression was the most common psychiatric illness appearing before epilepsy onset in 10 (9.7%) patients, and 12 (11.65%) patients were currently taking antidepressants. Previous use of AEDs considered inappropriate for JME did not influence the current response to VPA ($p=0.723$). Relapses due to poor compliance occurred more often in patients with persistent seizures ($p<0.001$).

3.2. Results of treatment

Forty-six (44.7%) patients were seizure free for at least one year, while 57 (55.3%) had persistent seizures; nevertheless, 76 (73.7%) patients were free from GTC seizures.

Myoclonias were the most frequently persistent seizure type in all patients (49/47.6%). Absence persisted in four (3.88%) patients, and no patient persisted with astatic seizures.

Relapses due to poor adherence to AED schedule occurred in 71 (68.9%) patients. This was the most common trigger factor for breakthrough seizures. Sleep deprivation was the second most common trigger, found in 66 (64.1%) patients, followed by stress in 39 (37.9%) patients, fatigue in 35 (34%) patients, menstruation in 11 (10.7%) patients, alcohol use in nine (8.7%) patients, photic stimulation in seven (6.8%) patients, and fasting in five (4.9%) patients.

3.3. Comparisons between low versus high dose of valproate (see Table 1)

The median dose of VPA used for all patients was 1,091.26 mg $\pm$ 370 (range 400–2,400 mg). Forty-eight patients (40.4%) were taking low doses of VPA (< 1000). There were no statistically significant differences in seizure freedom between patients taking a low dose of VPA versus patients taking a high dose of VPA ($p=0.535$) (Figure 1). The seizure-free time in patients taking a low dose averaged 9.09 ± 7.39 years, and seizure freedom averaged 6.33 ± 5.2 years among patients taking a high dose ($p=0.065$).

We performed a comparison to determine if there were differences in VPA dose in patients free of GTC versus those with persistent GTC. No significant difference was found regarding the persistence of GTC and VPA dose ($p=0.749$).

We did a further comparison to determine if there were clinical differences between patients taking a low dose of VPA versus those taking a high dose, with special attention to gender and weight, as those variables could be related to VPA dose. However, no statistically significant differences were found when comparing clinical characteristics between groups, except for the presence of thyroid disease, which was associated with the use of higher VPA doses ($p=0.015$).

3.4. Comparisons between low versus high blood levels of valproate (see Table 2)

The average blood level of VPA was 73.08 mcg/dl $\pm$ 28.36 (range 0.8–148 mcg/dl. Only 22 patients (22.6%) had low blood levels (< 50).

We found no statistically significant differences in seizure freedom when comparing patients with low blood VPA levels versus patients with high blood VPA levels ($p=0.690$) (Figure 1).

The seizure-free time in patients with low blood levels averaged 7.29 ± 7.56 years; among patients with high blood levels, it was 7.58 ± 6.06 years ($p=0.871$).

No significant difference was found regarding the persistence of GTC seizures in patients having high or low VPA blood levels ($p=0.899$).

When comparing clinical characteristics between groups, there were no statistically significant differences, except for patients who were taking antidepressants, who had lower VPA blood levels ($p=0.019$).

Finally, we divided the patients into four groups according to VPA dose and blood level: 1) high dose and high blood level, 2) low dose and low blood level, 3) high dose and low blood level, and 4) low dose and high blood level. No significant differences were found between the four groups ($p= 0.755$) (Figure 2). Patients in groups 1 and 2 had levels that were

concordant with the VPA daily dose they were taking, whereas patients in group 3 could have been non-compliant and patients in group 4 could have been slow metabolizers of VPA.

3.5. Risk factors for persistent seizures in patients with JME taking VPA monotherapy (see Table 3)

An analysis to determine which clinical characteristics were related to persistence of seizures was performed, but no differences were seen between patients completely seizure free versus those with persistent seizures. No differences in mean VPA dose or mean blood VPA levels were seen between groups. Previous use of AEDs considered inappropriate for JME did not influence the current response to VPA ($p=0.723$). Relapses due to poor compliance occurred more often in patients with persistent seizures ($p<0.001$).

4. Discussion

A previous trial in patients with JME comparing a low dose versus a high dose demonstrated good seizure control using a low dose (500 mg); however, these authors used VPA along with clonazepam in the low-dose group.²²

Although the VPA dose that is considered adequate and therapeutic is between 1000 and 2000 mg per day, and the defined daily dose by the WHO is 1500 mg of VPA³⁰, some studies have reported seizure control with doses of 400 to 500 mg per day.²¹⁻²² A recent trial demonstrated seizure freedom in 78% of patients with JME using a low dose of VPA (<600 mg/day).³¹

In our study, no difference in seizure control was observed between the use of doses less than or equal to 1000 mg VPA versus higher doses of VPA. We did not find differences either when comparing low and high VPA blood levels and seizure control. No differences were seen in age, sex, or weight among patients with low doses or low blood levels compared to those with high doses or high blood levels of VPA.

It should be noted that almost half of our patients were taking a low VPA dose, but only one third had low blood levels—which means most of our patients with JME achieved good VPA blood levels despite taking a low dose of VPA. We should also be aware that pharmacogenomic factors may modify the response to AEDs in up to 30% of patients³²; our patients might be slow metabolizers and therefore achieve therapeutic blood levels with low AEDs dosage. Since our patients with JME were able to reach good blood levels by taking low VPA doses, it should be determined if this was particular to our population. Thus, these results might not be extrapolated to other patients with JME.

Furthermore, our study could not define the reason(s) why some patients responded adequately to a low dose and/or low blood VPA levels and remained seizure free for several years. As it was a retrospective study, we were unable to determine if patients were initially treated with a low dose of VPA and then scaled to a higher dose due to persistence of seizures, especially GTC. However, as the treating physicians of these patients, we agreed that we usually started our patients with a therapeutic VPA dose, such as that defined by the WHO. Over time we were able to decrease the VPA dose due to complete seizure freedom

or freedom from GTC seizures. We also could not find the reasons why some patients continued and persisted with seizures despite adequate and high VPA doses and/or high therapeutic blood levels.

Drug resistance in JME has been associated with (a) evolution from childhood absence epilepsy, (b) earlier onset of the disease, (c) psychiatric disorders, and (d) the presence of thyroid dysfunction.^{21,28, 33,34,35} Other studies have found that asymmetric EEG features such as focal spikes and sharp waves, as well as intellectual impairment, were poor prognostic factors for VPA treatment.^{37,38}

In our study, we could not relate any clinical characteristics to the persistence of seizures in patients with JME undergoing VPA monotherapy. We could not find a correlation between poor seizure control and the previous use of AEDs that aggravated seizures, in contrast to the findings of Geithner and colleagues.³⁶ Neither the history or the presence of thyroid disease was related to lack of seizure control in our study.³⁴ We only found that patients taking a higher dose of VPA had more thyroid abnormalities compared to those taking a low dose. We also could not statistically associate abnormal EEGs and abnormal MRIs with persistent seizures. We therefore failed to find clinical characteristics as risk factors for persistent seizures in patients with JME treated with VPA monotherapy. We believe pharmacogenomic and genetic factors, including major and minor genes, interacting with environmental factors might be the key to determine which patients will not respond adequately to VPA treatment.³⁴

It is possible that the group of patients with persistent seizures and low VPA blood levels presented “pseudoresistance” due to poor adherence to treatment and unhealthy lifestyle.³³ Some patients with high VPA doses and high therapeutic blood levels continued to have seizures; we called them “truly drug resistant,” or at least resistant to VPA. In our group of patients with drug resistance to VPA, we added a second or third AED. This was done in 27 (26.2%) patients where GTC seizures continued. However, it should always be established which patients relapse due to non-compliance or lifestyle, and are therefore “pseudoresistant,” and which relapse due to “true drug resistance.”

Because two neurologists/epileptologists in our epilepsy clinic provided the diagnosis of JME, we were confident of the accuracy of the JME diagnosis and made sure that seizures were not persisting due to focal extratemporal epilepsies or non-epileptic events that mimic JME.

Patients with JME and persistent myoclonias or absences as their only seizure type(s) refused to use combination AED therapy since they were free from GTC seizures; they chose instead to continue with VPA monotherapy. Patients who did not have GTC seizure freedom with VPA despite high doses or high serum levels are currently undergoing monotherapy with other drugs or combination therapy.

With JME, patients, relatives, and their treating physicians are usually more concerned about the persistence of GTC seizures than persistence of myoclonias or absences. We need to find out why some patients attain freedom from seizures with a low dose of VPA. Interestingly, the relapse rate is high in these patients when VPA is dropped.^{21, 22, 28, 34,39} We found

complete seizure freedom in only 46 (44.6%) patients. This low percentage of total seizure control could be due to the fact that we considered the presence of myoclonias or absences as incomplete control of seizures—unlike other studies, where seizure freedom was based on the absence of only GTC seizures. In addition, we are a referral center where patients with refractory epilepsy are most often seen.

Persistent GTC seizures were found as the only remaining seizure in 26.2% of our patients. Others have reported persisting GTC seizures between 18.6% and 45% in patients with JME.³⁵ Long-term outcome in JME is still controversial; recent studies described remission in 12%–28% of cases.^{34,36,40} It could be argued that our patients who are seizure free with either a low dose or low blood levels of VPA might be cured; so far, however, we have found that our patients with JME have a high frequency of relapses with the suspension of or poor adherence to treatment.²⁸

As this study was retrospective, some data were missing, such as information regarding the use of extended-release formulations. Prospective studies should be performed in patients with JME that address dose intervals and comparisons between regular versus extended-release formulations. Though we did not describe side effects or compliance, it should be taken into account that low doses lead to warrant better compliance and fewer side effects. In our study, we saw a tendency for longer seizure freedom time in patients taking a low dose of VPA.

5. Conclusion

In patients with JME, we propose to use low doses of VPA (500 to 1000 mg) for initial treatment, and to evaluate to determine if complete freedom from seizures is attained. If not, VPA dose can be increased gradually until adequate control of seizures is achieved, understanding that myoclonias are the seizure type that most frequently persist despite high doses and high blood levels of VPA, and taking into account factors for drug resistance in JME.

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References

1. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010; 51:676–685. [PubMed: 20196795]
2. Nicoletti A, Reggio A, Bartoloni A, Failla G, Sofia V, Bartalesi F, et al. Prevalence of epilepsy in rural Bolivia: a door-to-door survey. *Neurology*. 1999; 10:2064–69. 53. [PubMed: 10599782]

3. Hauser, WA. Epidemiology of epilepsy in children. In: Pellock, JM.; Dobson, WE.; Bourgeois, BFD., editors. *Pediatric Epilepsy: Diagnosis and Therapy*. 2nd. New York: Demos; 2001. p. 87-8.
4. Janz, D.; Christian, W. Impulsive petit-mal. *Z Nervenheilk.* In: Malafosse, A.; Genton, P.; Hirsch, E.; Marescaux, C.; Broglin, D.; Bernasconi, R., editors. *Idiopathic generalised epilepsies*. Vol. 176. London: John Libbey & Co. Ltd; 1957. 1994. p. 346-386.p. 229-251.(Translated into English by P Genton)
5. Delgado-Escueta AV, Enrile-Bacsal F. Juvenile myoclonic epilepsy of Janz. *Neurology*. 1984; 34:285–294. [PubMed: 6422321]
6. Asconapé J, Penry JK. Some clinical and EEG aspects of benign juvenile myoclonic epilepsy. *Epilepsia*. 1984; 25:108–14. [PubMed: 6420145]
7. Penry JK, Dean JC, Riela AR. Juvenile myoclonic epilepsy: long term response to therapy. *Epilepsia*. 1989; 30(Suppl 4):S19–23. [PubMed: 2506007]
8. Auvin S. Treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy. *Neuropsychiatr Dis Treat*. 2007; 3:729–34. [PubMed: 19300607]
9. Buchanan N. The use of lamotrigine in juvenile myoclonic epilepsy. *Seizure*. 1996; 5:149–51. [PubMed: 8795132]
10. Morris GL, Hammer AE, Kustra RP, Messenheimer JA. Lamotrigine for patients with juvenile myoclonic epilepsy following prior treatment with valproate: results of an open label study. *Epilepsy Behav*. 2004; 5:509–12. [PubMed: 15256187]
11. Noahctar S, Andermann E, Meyvish P, Andermann F, Gough WB, Schieman-Delgado J, N166 Levetiracetam study group. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. *Neurology*. 2008; 70:607–16. [PubMed: 18285535]
12. Sousa Pda S, Araújo Filho GM, Garzon E, Sakamoto AC, Yacubian EM. Topiramate for the treatment of juvenile myoclonic epilepsy. *Arq Neuropsiquiatr*. 2005; 63:733–37. [PubMed: 16258645]
13. Biton V, Bourgeois BF; YTC/YTCE Study Investigators. Topiramate in patients with juvenile myoclonic epilepsy. *Arch Neurol*. 2005; 62:1705–8. [PubMed: 16286543]
14. Levisohn PM, Holland KD. Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison. *Epilepsy Behav*. 2007; 10:547–52. [PubMed: 17482520]
15. Kothare SV, Valencia I, Khurana DS, Hardison H, Melvin JJ, Legido A. Efficacy and tolerability of zonisamide in juvenile myoclonic epilepsy. *Epileptic Disord*. 2004; 6:267–70. [PubMed: 15634623]
16. Afra P, Adamolekun B. Lacosamide treatment of juvenile myoclonic epilepsy. *Seizure*. 2012; 21:202–4. [PubMed: 22281192]
17. Calleja S, Salas-Puig J, Ribacoba R, Lahoz CH. Evolution of juvenile myoclonic epilepsy treated from the outset with sodium valproate. *Seizure*. 2001; 10:424–7. [PubMed: 11700996]
18. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013; 54:551–63. [PubMed: 23350722]
19. Velez-Ruiz NJ, Meador KJ. Neurodevelopmental effects of fetal antiepileptic drug exposure. *Drug Saf*. 2015; 38:271–8. [PubMed: 25693658]
20. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalized and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007; 369:1016–26. [PubMed: 17382828]
21. Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5 year prospective study. *Epilepsia*. 1994; 35:285–96. [PubMed: 8156946]
22. Karlovassitou-Koniari A, Alexiou D, Angelopoulos P, Armentsoudis P, Dimitrakoudi E, Delithanasis I, et al. Low dose sodium valproate in the treatment of juvenile myoclonic epilepsy. *J Neurol*. 2002; 249:396–99. [PubMed: 11967642]
23. Hitris N, Brodie MJ. Evidence-based treatment of idiopathic generalized epilepsies with older antiepileptic drugs. *Epilepsia*. 2005; 46(Suppl 9):149–53. [PubMed: 16302889]
24. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as

- initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2006; 47:1094–120. [PubMed: 16886973]
25. Sundqvist A, Tomson T, Lundkvist B. Valproate as monotherapy for juvenile myoclonic epilepsy: dose-effect study. *Ther Drug Monit*. 1998; 20:149–57. [PubMed: 9558128]
 26. Jara-Prado A, Martínez-Juárez IE, Ochoa A, González VM, Fernández-González-Aragón M del C, López-Ruiz M, et al. Novel Myoclonin1/EFHC1 mutations in Mexican patients with juvenile myoclonic epilepsy. *Seizure*. 2012; 21:550–4. [PubMed: 22727576]
 27. Betting LE, Mory SB, Lopes-Cendex I, Li LM, Guerreiro MM, Guerreiro CA, et al. EEG features in idiopathic generalized epilepsy: clues to diagnosis. *Epilepsia*. 2006; 47:523–8. [PubMed: 16529616]
 28. Martínez-Juárez IE, Alonso ME, Medina MT, Durón RM, Bailey JN, López-Ruiz M, et al. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. *Brain*. 2006; 129:1269–80. [PubMed: 16520331]
 29. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010; 51:1069–77. [PubMed: 19889013]
 30. World Health Organization. Guidelines for ATC classification and defined daily dose assignment. Geneva: WHO; 1996.
 31. Miró J, Aiguabella M, Veciana M, Juvany R, Santurino M, Leiva E, et al. Low-dose sodium valproate in the treatment of idiopathic generalized epilepsies. *Acta Neurol Scand*. 2014; 129:e20–3. [PubMed: 24372179]
 32. López M, Dorado P, Monroy N, Alonso ME, Jung-Cook H, Machín E, et al. Pharmacogenetics of the antiepileptic drugs phenytoin and lamotrigine. *Drug Metabol Drug Interact*. 2011; 26:5–12. [PubMed: 21557672]
 33. Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiatry*. 2001; 70:240–3. [PubMed: 11160477]
 34. Baykan B, Altindag EA, Bebek N, Ozturk AY, Aslantas B, Gurses C, et al. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. *Neurology*. 2008; 70:2123–9. [PubMed: 18505992]
 35. Guaranha MS, Filho GM, Lin K, Guilhoto LM, Caboclo LO, Yacubian EM. Prognosis of juvenile myoclonic epilepsy is related to endophenotypes. *Seizure*. 2011; 20:42–8. [PubMed: 21041102]
 36. Geithner J, Schneider F, Wang Z, Berneiser J, Herzer R, Kessler C, et al. Predictors for longterm seizure outcome in juvenile myoclonic epilepsy: 25-63 years of follow up. *Epilepsia*. 2012; 53:1379–86. [PubMed: 22686598]
 37. Fernando-Dongas MC, Radtke RA, VanLandingham KE, Husain AM. Characteristics of valproic acid resistant juvenile myoclonic epilepsy. *Seizure*. 2000; 9:385–8. [PubMed: 10985993]
 38. Szaflarski JP, Lindsell CJ, Zakaria T, Banks C, Privitera MD. Seizure control in patients with idiopathic generalized epilepsies: EEG determinants of medication response. *Epilepsy Behav*. 2010; 17:525–30. [PubMed: 20227351]
 39. Sokic D, Ristic AJ, Vojvodic N, Jankovic S, Sindjelic AR. Frequency, causes and phenomenology of late seizure recurrence in patients with juvenile myoclonic epilepsy after a long period of remission. *Seizure*. 2007; 16:533–7. [PubMed: 17574449]
 40. Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: A population based study. *Neurology*. 2009; 73:1041–5. [PubMed: 19786695]

Highlights

- Valproate seems to be the drug of choice for the treatment of juvenile myoclonic epilepsy (JME), with special considerations for childbearing women.
- We found no significant differences between valproate low dose (1,000 mg or lower) and high dose regarding seizure freedom in patients with JME.
- We found no significant difference between valproate low blood levels (50 mcg/dl) and high blood levels regarding seizure freedom in patients with JME.
- It could be appropriate to start with a low dose of valproate in patients with JME and to scale the dose when necessary to attain seizure freedom.

Figure 1.

Results of treatment with valproate in patients with juvenile myoclonic epilepsy.

A. Seizure control in patients taking low valproate dose compared to patients taking high valproate dose.

B. Seizure control in patients taking low valproate compared to patients taking high valproate blood levels.

C. Comparison between mean valproate doses in patients with juvenile myoclonic epilepsy regarding seizure control.

D. Comparison between mean valproate blood levels in patients with juvenile myoclonic epilepsy regarding seizure control.

Figure 2. Seizure freedom in patients with juvenile myoclonic epilepsy Comparison between valproate dose and blood level in patients with juvenile myoclonic epilepsy regarding seizure control.

Table 1
Comparisons between clinical characteristics of patients with juvenile myoclonic epilepsy taking low valproate dose versus patients taking high valproate dose

Clinical characteristics	Low VPA dose (1000 mg/d)	High VPA dose (>1000md/d)	p-value
Age of onset	13.7 (±3)	13.5 (±2.9)	0.805
Current Age	29.13 (± 7.6)	27.84 (± 7.3)	0.384
Weight	66.7 (± 12.14)	71.55 (± 16.9)	0.107
Gender			
Male	18 (38.3%)	29 (61.7%)	0.122
Female	30 (53.7%)	26 (46.3%)	
Perinatal complications			
Present	12 (25%)	10 (10%)	0.683
Absent	34 (70.8%)	43 (78.2%)	
Unknown	2 (4.2%)	2 (3.6%)	
Febrile seizures			
Present	2 (4.2%)	2 (3.6%)	0.817
Absent	41 (85.4%)	45 (81.8%)	
Unknown	5 (10.4%)	8 (14.5%)	
Family history of epilepsy			
Present	24 (50%)	32 (58.2%)	0.406
Absent	24 (50%)	23 (41.8%)	
Electroencephalogram			
Normal	29 (60.4%)	26 (47.3%)	0.182
Abnormal	19 (39.6%)	29 (52.7%)	
Subsyndrome			
Classic JME	40 (38.8%)	46 (44.4%)	0.967
Other subsyndrome	8 (7.8%)	9 (8.7%)	
Neuroimaging			
Normal	22 (45.8%)	27 (49.1%)	0.877
Abnormal	20 (41.7%)	23 (41.8%)	
Unknown	6 (12.5%)	5 (9.1%)	
Previous use of inappropriate AEDs			
No	20 (41.7%)	23 (41.8%)	0.988
Present	28 (58.3%)	32 (58.2%)	
Years taking VPA	8.8 (±7.05)	6.83 (±5.9)	0.129
Thyroid disease			
Present	1 (2.1%)	9 (16.3%)	0.015
Absent	40 (83.3%)	33 (60%)	
Unknown	7 (14.6%)	13 (23.6%)	
Use of antidepressants			

Clinical characteristics	Low VPA dose (1000 mg/d)	High VPA dose (>1000md/d)	p-value
Present	7 (14.6%)	5 (9.1%)	0.386
Absent	41 (85.4%)	50 (90.9%)	
Seizure outcome			
Seizure freedom	23 (47.9%)	23 (41.8%)	0.535
Persistent seizures	25 (52.1%)	32 (58.2%)	
Persistent Generalized tonic clonic seizures			
Present	12 (25%)	15 (27.3%)	0.794
Absent	36 (75%)	40 (72.7%)	
Relapses due to non compliance			
Present	33 (68.8%)	38 (69%)	0.870
Absent	14 (29.2%)	15 (27.27%)	
Unknown	1 (2%)	2 (3.63%)	

VPA= valproate; AEDs= antiepileptic drugs

Table 2
Comparisons between clinical characteristics of patients with juvenile myoclonic epilepsy with low valproate blood levels versus patients with high valproate blood levels

Clinical characteristics	Low VPA blood levels (≤ 50 mcg)	High VPA blood levels (> 50 mcg)	p-value
Age of onset	13.7 ($\pm$ 3.3)	13.62 ($\pm$ 2.9)	0.155
Current Age	28 ($\pm$ 9)	28.5 ($\pm$ 7.02)	0.791
Weight	69.7 ($\pm$ 18.3)	69.2 ($\pm$ 14)	0.908
Gender			
Male	10 (45.5%)	37 (45.7%)	0.985
Female	12 (54.5%)	44 (54.3%)	
Perinatal complications			
Present	5 (22.7%)	17 (21%)	0.965
Absent	16 (72.7%)	61 (75.3%)	
Unknown	1 (4.5%)	3 (3.7%)	
Febrile seizures			
Present	2 (9.1%)	2 (2.5%)	0.349
Absent	17 (77.3%)	69 (85.2%)	
Unknown	3 (13.6%)	10 (12.13%)	
Family history of epilepsy			
Present	11 (50%)	45 (55.6%)	0.643
Absent	11 (50%)	36 (44.4%)	
Electroencephalogram			
Normal	11 (50%)	44 (54.3%)	0.719
Abnormal	11 (50%)	37 (45.7%)	
Subsyndrome			
Classic JME	18 (17.5%)	68 (66%)	0.811
Other subsyndrome	4 (3.9%)	13 (12.6%)	
Neuroimaging			
Normal	9 (49.4%)	40 (49.4%)	0.563
Abnormal	10 (45.4%)	33 (40.7%)	
Unknown	3 (13.6%)	8 (9.9%)	
Previous inappropriate AEDs			
None	7 (31.8%)	36 (44.4%)	0.287
Present	15 (68.2%)	45 (55.6%)	
Years using VPA	6.73 ($\pm$ 6.8)	8.06 ($\pm$ 6.4)	0.401
Thyroid disease			
Present	2 (9%)	8 (9.4%)	1.000
Absent	17 (77.3%)	56 (61.12%)	
Unknown	3 (13.6%)	17 (21%)	
Use of antidepressants			

Clinical characteristics	Low VPA blood levels (≤ 50 mcg)	High VPA blood levels (> 50mcg)	p-value
Present	6 (27.3%)	6 (7.4%)	0.019
Absent	16 (72.7%)	75 (92.6%)	
Seizure outcome			
Seizure freedom	9 (40.9%)	37 (45.7%)	0.690
Persistent seizures	13 (59.1%)	44 (54.3%)	
Persistent Generalized tonic clonic seizures			
Present	6 (27.3%)	21 (25.9%)	0.899
Absent	16 (72.7%)	60 (74.1%)	
Relapses due to non compliance			
Present	17 (77.3%)	54 (66.7%)	0.258
Absent	4 (18.2)	25 (30.9%)	
Unknown	1 (4.5%)	2 (2.4%)	

VPA= valproate; AEDs= antiepileptic drugs

Table 3
Risk factors for persistent seizures in patients with juvenile myoclonic epilepsy taking valproate monotherapy

Clinical characteristics	Seizure free	Persistent seizure	p-value
Gender			
Male	20 (43.5%)	27 (47.4%)	0.694
Female	26 (56.5%)	30 (52.6%)	
Age onset	13.91 (±3.025)	13.44 (±2.910)	0.425
Epilepsy duration	14.96 (±9.35)	14.65 (±7.73)	0.856
Family history of epilepsy			
Present	25 (54.3%)	31 (54.4%)	0.535
Absent	21 (45.7%)	26 (45.6%)	
Perinatal complications			
Present	8 (17.4%)	14 (24.6%)	0.339
Absent	35 (76.1%)	42 (73.7%)	
Unknown	3 (6.5%)	1 (1.8%)	
Febrile seizures			
Present	2 (4.3%)	2 (3.5%)	1.000
Absent	38 (82.6%)	48 (84.2%)	
Unknown	6 (13%)	7 (12.3%)	
Previous psychiatric disease			
Present	2 (4.3%)	8 (14%)	0.179
Absent	44 (95.7%)	49 (86%)	
Use of antidepressant			
Present	6 (13%)	6 (10.5%)	0.692
Absent	40 (87%)	51 (89.5%)	
Previous inappropriate AEDs			
None	18 (39.1%)	25 (43.9%)	0.628
Present	28 (60.9%)	32 (56.1%)	
Non compliance relapses			
Present	23 (50%)	48 (84.2%)	<0.0001
Absent	23 (50%)	9 (15.8%)	
Electroencephalogram			
Normal	28 (60.9%)	27 (47.4%)	0.172
Abnormal	18 (39.1%)	30 (52.6%)	
Abnormal EEG			
Typical	8/23 (44.4%)	15/23 (50%)	0.709
Atypical	10/23 (35.6%)	15/23 (50%)	
Neuroimaging			
Normal	20 (43.5%)	29 (50.9%)	0.440

Clinical characteristics	Seizure free	Persistent seizure	p-value
Abnormal	21 (45.7%)	22 (38.6%)	
Unknown	5 (10.9%)	6 (10.5%)	
Subsyndrome			
Classic JME	34 (73.9%)	52 (91.2%)	0.031
Other subsyndrome	12 (26.1%)	5 (8.8%)	
Mean VPA dosage	1,104. 35(± 401)	1,080. 70 (± 346)	0.749
Mean VPA blood levels	72.79 (± 25)	73. 31 (± 30)	0.926
Seizure Types			
MS only	2 (4.3%)	1 (1.8%)	
MS + GTCS	19 (41.3%)	26 (45.6%)	
MS + ABS	1 (2.2%)	1 (1.8%)	0.155
MS + ABS + GTCS	15 (32.6%)	27 (47.4%)	
MS + Ast	2 (4.3%)	0 (0%)	
MS + Ast + GTCS	6 (13%)	1 (1.8%)	
MS + Ast + GTCS + ABS	1 (2.2%)	1 (1.8%)	

AEDs= antiepileptic drugs; VPA= valproate; JME =Juvenile myoclonic epilepsy; MS= myoclonias; GTC= generalized tonic-clonic seizures; ABS= absences; Ast= atstatic seizures.