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# Retrospective study of topiramate in a paediatric population with intractable epilepsy showing promising effects in the West syndrome patients

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*Abstract*

*Topiramate (TPM) is a new anti-epileptic drug with proven efficacy against partial seizures in adults. Its use in children is less well documented. In a retrospective study, 41 patients with intractable childhood epilepsy were treated with TPM as add-on therapy for an average period of 15 months. They were classified according to seizure type and etiology. The dose was titrated for effect and ranged between 2 and 24 mg/kg/d. Of the 41 patients being treated, six became seizure free, ten had a seizure reduction of more than 75% and eight a seizure reduction of between 50 and 75%. The most remarkable effect was seen in seven patients with West syndrome. Of these, four patients became seizure free and one had more than 75% seizure reduction. Adverse effects including sedation, fatigue, difficulties with verbal expression and anorexia were noted in 15 patients. None of these effects were important enough to interrupt treatment. We conclude that TPM as adjunctive therapy is a promising drug in children with intractable epilepsy, especially in the patients with West syndrome.*

*Key words* : Topiramate ; Epilepsy ; Children ; West syndrome ; Infantile spasms.

*Abbreviations* : TPM = Topiramate ; ACTH = Adrenocorticotrope hormone

## Introduction

Topiramate (TPM) is a new anti-epileptic drug with a broad range of anti-epileptic activity. It acts through blocking of voltage dependent sodium channels, antagonism of a kainate subtype of the glutamate receptor, enhancing of GABA-stimulated chloride influx and inhibition of erythrocyte carbonic anhydrase (Glauser, 1999 ; Pellock, 1999). In adults, the effectiveness of TPM as monotherapy or as adjunctive therapy for refractory partial-onset seizures and as adjunctive therapy for primary generalized seizures has been well established (Bison *et al*., 1997 ; Reife and Pledger, 1997 ; Glauser, 1999). Open studies and reports on the use of TPM in children demonstrated that TPM is a useful therapy in pediatric patients with intractable childhood epilepsy (Glauser, 1997 ; Elterman *et al*., 1999 ; Moreland *et al*., 1999 ; Uldall and Buchholt, 1999 ; Yeung *et al*., 2000). To our knowledge, only one study so far has clearly demonstrated the positive effect of a treatment with TPM in infants with infantile spasms (Glauser *et al*., 1998 ; Glauser *et al*., 2000a). Here we report the results of treatment with TPM in 41 children, including 7 patients with West syndrome.

## Patients and methods

In a retrospective study, the use of TPM as add-on therapy in children with intractable childhood epilepsy was studied in the pediatric neurology unit at the University Hospital Ghent. Between spring 1998 and spring 2000 we treated 41 children with TPM, 21 boys and 20 girls. They were classified by seizure type, or syndrome, and by etiology (Table 1 and Table 2). Twenty children had partial onset seizures, three severe myoclonic epilepsy in infancy, two myoclonic astatic epilepsy, one primary Lennox-Gastaut syndrome. Five patients had multiple types of seizures. Seven patients had West syndrome (Table 2, patients 35-41). We considered a patient as having West syndrome when he/she had infantile spasms, hypsarrhythmia on EEG, and regression of development. The underlying cause in the patients with West syndrome was specified. All patients with West syndrome had received or continued to receive vigabatrine when TPM was started. Changes on EEG registration were retrospectively evaluated. One patient (patient 14) had presented with West syndrome at the age of 7 months, later evolving to a refractory epilepsy with predominantly tonic-clonic seizures.

The age of all patients included in this series ranged from 1 to 22 years, with a mean age of 7,7 years. In 26 patients, seizures had started within the first year of life. The mean age at seizure onset was 16 months and TPM was started at a mean age of 5,8 years, ranging from 3 months to 21 years.

In each patient, between one and seven anti-epileptic drugs had been tried before TPM was started. TPM was used as add-on therapy. It was started at a dose of 1-2 mg/kg/d and titrated to effect. The dose was increased with 1-2 mg/kg/d every one to two weeks until effect was seen on

Table 1

Clinical characteristics of the patients treated with TPM, except those with West syndrome

| Pt # | Age (years) | Age at seizure onset | Etiology | Seizure type | Seizure syndrome | Concomitant anti epileptic drugs |
|---|---|---|---|---|---|---|
| 1 | 9 | 8 years | Unknown | | Lennox-Gastaut | VPA,LMT,NTZ |
| 2 | 13 | 17 months | Unknown | | Myoclonic astatic | VPA,NTZ |
| 3 | 5 | 6 months | Perinatal asphyxia | CP,MYO,AT | | VPA,CBZ,VGB |
| 4 | 10 | 7 months | Hippocampal atrophy | T,MYO,AT,ABS,TC | | CBZ,VGB |
| 5 | 11 | 3 years | Unknown | CP | | LMT,ETS |
| 6 | 7 | 13 months | Encephalitis | CP | | VGB,FB,CLB |
| 7 | 10 | 4 months | Tuberous sclerosis | CP | | CBZ,VGB |
| 8 | 7 | 2 years | Traumatic | CP | | CBZ |
| 9 | 18 | 7 years | Unknown | CP | | LMT,FB |
| 10 | 2 | 3 months | Unknown | CP | | VPA,CNZ,VGB |
| 11 | 9 | 18 months | Ischemic lesion | CP | | CBZ,CLB |
| 12 | 11 | 3 months | Migration disorder | SP | | CBZ,VGB |
| 13 | 9 | 20 months | Hippocampal sclerosis | SP | | NTZ,SLT |
| 14 | 11 | 7 months | Unknown | TC | | VPA,ETS,NTZ |
| 15 | 16 | 3 years | Migration disorder | | Myoclonic astatic | PH,PB |
| 16 | 6 | 2 years | Unknown | GEL,MYO,AT,ABS,TC | VPA,LMT | |
| 17 | 4 | 5 months | Unknown | CP,SP | | VPA,FB |
| 18 | 11 | 2 years | Unknown | CP,T,AT | | VPA,CBZ |
| 19 | 6 | 3 months | Tuberous sclerosis | CP,SE,ABS,TC | | CBZ,VGB |
| 20 | 5 | 4 months | Tuberous sclerosis | CP | | VPA,VGB |
| 21 | 22 | 4 months | FDU | CP | | CBZ,CNZ |
| 22 | 9 | 7 months | Unknown | CP | | VPA |
| 23 | 1 | 4 months | Unknown | CP | | LMT |
| 24 | 8 | 4 years | Polymicrogyria | CP | | CBZ,VGB |
| 25 | 10 | 10 months | Unknown | CP | | CBZ,CNZ,NTZ |
| 26 | 5 | 2 years | Perinatal asphyxia | CP | | CBZ,VGB |
| 27 | 17 | 17 months | Unknown | SP | | CBZ,VGB |
| 28 | 6 | 3 months | Sturge-Weber | SP | | CBZ,VGB |
| 29 | 7 | 8 months | Encephalitis | SP | | VPA,CNZ,ETS,NTZ |
| 30 | 2 | 6 months | Unknown | | SMEI | CBZ,ETS,PH,NTZ |
| 31 | 4 | 7 months | Unknown | | SMEI | VPA |
| 32 | 2 | 11 months | Unknown | | SMEI | CBZ,LMT |
| 33 | 15 | 3 years | Unknown | TC | | LMT |
| 34 | 1 | 1 month | Unknown | T | | VPA,CNZ,VGB,ACTH |

Patient 1-13 discontinued treatment
Patient 14-34 are continuing treatment
FDU : familial degenerative disorder of unknown origin

TC : tonic-clonic
T : tonic
ABS : absence
AT : atonic
MYO : myoclonic
SP : simple partial
CP : complex partial
GEL : gelastic
SE : status epilepticus
SMEI : severe myoclonic epilepsy in infancy

CBZ : carbamazepine
CNZ : clonazepam
VPA : valproate
VGB : vigabatrin
LMT : lamotrigine
ETS : ethosuximide

PH : phenytoin
NTZ : nitrazepam
PB : phenobarbital
FB : felbamate
CLB : clobazam
SLT : sulthiame
ACTH : adrenocortico-trope hormone

seizure frequency. In most of the patients, the dose was augmented to 6 mg/kg/d. When seizures persisted for more than two to four weeks, the dose of TPM was further increased. Finally, the mean dose administered was 9,6 mg/kg/d, with a minimum of 2 mg/kg/d and maximum of 24 mg/kg/d. Concomitant anti- epileptic drugs and eventual discontinuance of any of these drugs were noted. Two patients (patient 34 and 37) were included who also received a treatment with adenocorticotrope hormone (ACTH) shortly after the start of TPM because of life threatening seizures. They continued their treatment with TPM after disruption of the ACTH treatment.

Seizure frequency was established before and after treatment with TPM. This was done by means of seizure diaries, when available, and by parental assessment of seizure frequency. A scale for change in seizures frequency was used : 4 represented freedom from seizures, 3 a reduction of more than 75%, 2 a reduction of 50 to 75%, 1 a reduction of less than 50%, 0 no change and -1 an increase in seizure frequency. Reported beneficial effects as well as adverse effects were noticed.

Table 2

West syndrome patients

| | |
|---|---|
| 35 | IS, hypsarrhythmia on EEG and developmental regression at age 3 months. Etiology : unknown (metabolic cause suspected because of retinal dystrophy). Treatment with VGB and PB without success. Start TPM 9 months after seizure onset. Dose augmented to 11 mg/kg/d. No effect on seizure frequency. EEG 9 months after start TPM showed frequent multifocal epileptiform discharges. No progression of development. Stop TPM after 9 months. Last follow-up at age 2 years. |
| 36 | IS, hypsarrhythmia on EEG and developmental regression at age 8 months. Etiology : MCAD deficiency.Treatment with VGB and VPA without success. Start TPM 1 month after seizure onset. Decrease of seizure frequency was seen a few days after augmenting the dose to 9 mg/kg/d. Seizure free at 11 mgtkg/d. Stop VPA after cessation of seizures. A few weeks later, progression of development. EEG was normal 7 months after start TPM. Last follow-up at age 2 years. |
| 37 | IS, hypsarrhythmia on EEG and developmental regression at age 6 months. Etiology : unknown. Treatment with VPA and VGB, without success. Start TPM 1 month after seizure onset without immediate success. Start ACTH 3 weeks later, in addition to TPM 5 mg/kg/d. Seizure free during ACTH treatment. Remained seizure free after cessation of ACTH (3 weeks later). A few weeks after cessation of spasms progression of development. EEG was normal 4 months after start TPM, 3 months after start ACTH. Last follow-up at age 2 years. |
| 38 | IS, hypsarrhythmia on EEG and developmental regression at age 3 months. Etiology : ischemic lesion in the region of the left arteria cerebri media. Treatment with VPA and VGB with partial success. Start TPM 5 months after seizure onset. Seizure free with TPM dose at 13 mg/kg/d, after cessation of VGB, 9 months after start TPM. A few weeks after cessation of spasms progression of development. EEG continues to show frequent spike waves over the left hemisphere. Last follow-up at age 1 years. |
| 39 | IS, hypsarrhythmia on EEG and developmental regression at age 6 months. Etiology : ischemic lesions in both hemispheres. Treatment with VPA and VGB with partial success. Start TPM 1 1/2 month after seizure onset. Seizure free few days after start TPM, at 2 mg/kg/d. VGB stopped. Six months after cessation of spasms progression of development. EEG 2 years after start of TPM showed focal epileptiform discharges. Last follow-up at age 2 years. |
| 40 | IS, hypsarrhythmia on EEG and developmental regression at age 4 months. Etiology : unknown. Treatment with VPA and VGB, with partial success. Start TPM 6 months after seizure onset. After 1-2 weeks, 50-75% reduction of seizure frequency ; after augmenting the dose to 15 mg/kg/d, more than 75% reduction. Progression of development in the following weeks. EEG 5 and 11 months after start of TPM showed slow background activity, diffuse epileptiform discharges. Last follow-up at age 2 years. |
| 41 | Convulsions from birth. Lack of developmental progression. IS, hypsarythmia on EEG at age 8 months. Etiology unknown. Treatment with VPA, VGB and NTZ, with partial success. Start TPM at the age of 12 months, dose increased to 8 mg/kg/d, with poor effect (<50%reduction). No improvement of development. EEG 2 months after start of TPM showed hypsarrhythmia, 5 months after start of TPM multifocal epileptiform discharges. Last follow-up at age 3 years. |

Patient 35 stopped treatment with TPM, patient 3641 are continuing
MCAD : medium-chain acylCoA dehydrogenase
IS : infantile spasms
VPA : valproate
VGB : vigabatrin
PB : phenobarbital
ACTH : adrenocorticotrope hormone
NTZ : nitrazepam

## Results

Of the 41 patients treated with TPM, six patients became seizure free, ten had more than 75% reduction of seizure frequency, eight between 50 and 75% and two less than 50%. In fifteen patients no change in seizure frequency was seen (Fig 1). None of the patients had an increase in seizure frequency.

The effect in the seven patients with West syndrome was remarkable (Fig 2, Table 2). Four patients became seizure free (patient 36, 37, 38 and 39) and one had a reduction in seizure frequency of more than 75% (patient 40). Two patients were bad responders with a reduction of less than 50%, or no effect (patient 41 and 35). In three of the patients who became seizure free, a specific etiology was known (Table 2). TPM was started one to five months following seizure onset in the four patients with West syndrome who ultimately became seizure free but only after 4 to 12 months in those who did not. When present, the reduction in seizure frequency occurred in a period of days after the appropriate dose of TPM was reached for that patient. In the patients who were good responders,

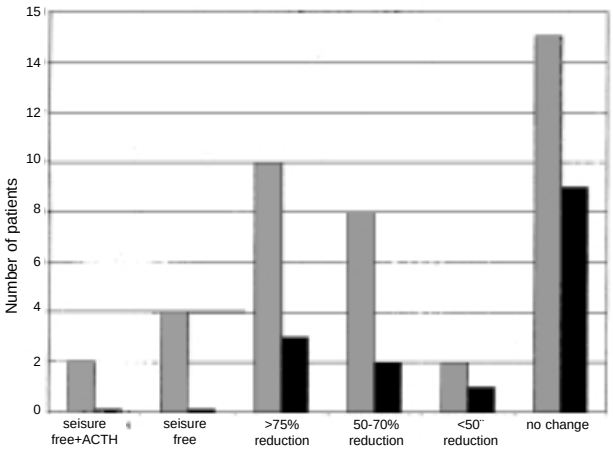


FIG 1. — Overall success of treatment with TPM in the patients studied (n = 41). The patients were grouped according to success of treatment. The light colored bars show the number of the patients in each group. The dark colored bars show the number of the patients in each group who experienced adverse effects.

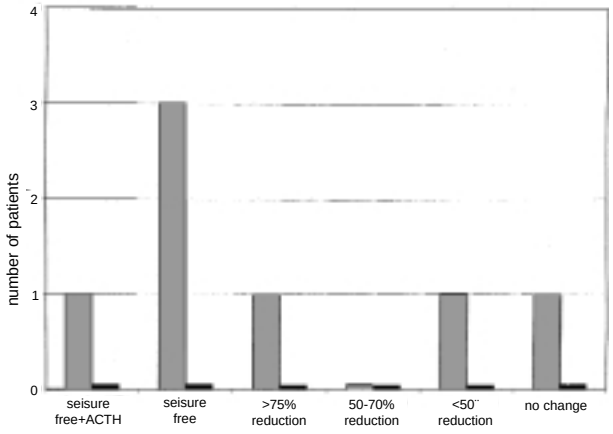


FIG 2. — Success of treatment in infants with West syndrome (n = 7). The light colored bars show the number of patients in each group. The dark colored bars show the number of the patients in each group

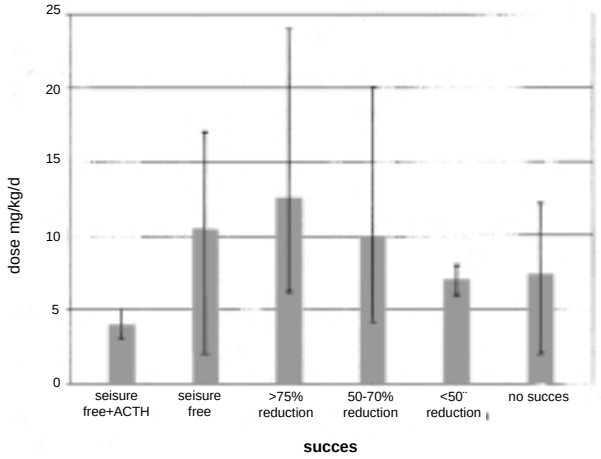


Fig 3. — Evaluation of the dose of TPM administered. The patients were grouped according to success of the treatment.

development started to improve during the following weeks. Only in one patient (patient 39) improvement of development became apparent only 6 months after the cessation of the seizures. One patient with West syndrome was also treated with ACTH because of life threatening seizures three weeks after TPM was started (1 month after seizure onset) (patient 37). He became seizure free during treatment with ACTH and remained seizure free after cessation of ACTH, while TPM was continued at the same dose. His psychomotor development improved soon after he became seizure free.

Hypsarrhythmia was seen on EEG before treatment in all the patients with West syndrome. EEG was not repeated at fixed time intervals following the start of TPM. This makes it impossible to evaluate the time delay between the start of TPM and the changes seen on EEG. In one patient who became seizure free (patient 36), a normalization of the EEG was seen. In two other patients who became seizure free, the EEG continued to show epileptiform discharges but no hypsarythmia. In the bad responders, the EEG remained severely disturbed with increased number of slow activities and frequent multifocal epileptiform alterations. In the patient who received also ACTH, the EEG was normal 4 months after the onset of TPM treatment.

One additional patient in this series was also treated with ACTH (patient 34). This patient presented with tonic seizures that did not respond to treatment with valproate, vigabatrin and clonazepam. When seizures became more severe TPM was started. Shortly thereafter, while TPM was still at a low dose, it was decided to add also ACTH because the frequency and the duration of the tonic seizures had increased and patient did not recover anymore between seizures. Under this treatment, the patient became seizure free and remained seizure free after cessation of ACTH. TPM dose at that moment was 3 mg/kg/d. Vigabatrin and clonazepam could be stopped later.

The effect of TPM in the patients with other types of seizures or seizure syndromes is shown in Table 3. In children with partial onset seizures (20 patients), only one became seizure free, four had more than 75% reduction of seizure frequency and five a 50 to 75% reduction.

In 14 patients, one or more of the concomitant anti-epileptic drugs could be stopped without subsequent increase in seizure rate. Two patients were placed on mono-therapy with TPM (patient 23 and 31). They both had a reduction in seizure frequency of > 75%. After discontinuing one or more of the concomitant anti-epileptic drugs in these 14 patients, the following combinations of anti-epileptic drugs were continued : eight patients received valproate, two patients nitrazepam, two patients ethosuximide, two patients vigabatrine and one patient carbamazepine in addition to TPM. Evaluation of success in function of the dose administered showed that a good response was obtained with low as well as high doses of TPM (Fig 3).

Beneficial effects can be seen in Table 4. Improvement in behavior, verbal communication, concentration and alertness were reported in 11 patients. Adverse effects were seen in 15 patients (Table 4). The most important were sedation, fatigue, difficulties with verbal expression and anorexia. Treatment with TPM was not interrupted in any of these patients because of the side effects. It is important to notice that 9 of the 15 patients who experienced side effects were bad responders to TPM while none of the patients who became seizure free had adverse effects (Fig 1), neither had the patients with West syndrome (Fig 2).

In the 25 patients who continued TPM, the mean duration of therapy at the end of our study was 15 months, with a maximum of 2 years and 4 months and a minimum of 9 months.

Table 3

Success of treatment with TPM in the patients studied, excluding the West syndrome patients

| | Succes | -1 | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| Seizure type | | | | | | | |
| Partial seizures<br>Tonic-clonic seizures<br>Tonic seizures<br>Multiple types | | | 9<br><br><br>2 | 1 | 5<br><br><br>2 | 4<br>2<br><br>1 | 1<br><br>1*<br> |
| Seizure syndrome | | | | | | | |
| SMEI<br>Myoclonic astatic seizures<br>Lennox-Gastaut syndrome | 1<br>2<br>1 | 2 | | | | | |
| Total | 0 | 14 | 1 | 8 | 9 | 2 | |

*SMEI* : severe myoclonic epilepsy of infants, * pt recieved also ACTH, *Change in seizure frequency* : -1 :increase ; 0 : no change ; 1 : reduction < 50% ; 2 : 50-75% reduction ; 3 : reduction > 75% ; 4 : freedom of seizures

## Discussion

Thirty nine percent of patients with intractable childhood epilepsy presented here had more than 75% reduction in seizure frequency or became seizure free on TPM. This indicates that TPM is an effective anticonvulsant therapy in children with drug resistant epilepsy. Our findings in children with intractable partial onset seizures, including simple partial and complex partial seizures, are consistent with previous reports (Elterman *et al*., 1997 ; Elterman *et al*., 1999 ; Moreland *et al*., 1999). Some authors suggest TPM as treatment in children for primary generalized tonic- clonic seizures, even in mono-therapy (Bison *et al*., 1997 ; Biton *et al*., 1999) and for Lennox-Gastaut syndrome (Sachdeo *et al*., 1999 ; Glauser *et al*., 2000b).

In the seven patients with West syndrome who were refractory to vigabatrine, treatment results were remarkable. Four patients became seizure free and one had more than 75% reduction of seizure frequency. These results are consistent with the results in one previous study on the effect of treatment with TPM in eleven children with infantile spasms (Glauser *et al*., 1998 ; Glauser *et al*., 2000a). Forty five percent of these children became seizure free and an additional 36% had a reduction in seizure frequency of more than 50%. These preliminary studies predict that TPM has the potential to become an important drug in the treatment of West syndrome. In our study, better results were obtained in the patients in whom TPM was started early after onset of the infantile spasms. The mean delay between onset of seizures and start of TPM was two months in the patients who responded favourably which contrasted with the mean delay of nine months in the bad responders. In all patients with positive effects on seizures, a significant progression of development was seen in the weeks following control of the seizures, except in one patient. The latter had extensive, bilateral cerebral lesions and the first signs of developmental progress were seen only after six months. As expected, the two patients who did not respond remained severely retarded. The beneficial effect of TPM in the West syndrome patients was confirmed by the results of the EEG studies. In half of the patients who became seizure free the EEG normalized in the months following seizure control. Absence of hypsarhythmia but persistence of focal epileptiform discharges were seen in the other half. In the two patients who did not respond to TPM, the EEG continued to show mulifocal epileptiform discharges.

Table 4

Beneficial effects and adverse side effects

| Beneficial effects | Number of patients |
|---|---|
| Alertness<br>Improved behavior<br>Improved verbal Communication<br>Improved Concentration | 9<br>6<br>7<br>4 |
| Total | 11 |
| Adverse effects | |
| Fatigue<br>Sedation<br>Nervousness<br>Diffficulties with verbal expression<br>Sleep disturbance<br>Aggression<br>Anorexia | 5<br>8<br>2<br>5<br>1<br>2<br>4 |
| Total | 15 |

In the patients included in this study, who ultimately became seizure free or had more than 75% reduction in seizure frequency, the mean dose of TPM was 10 mglkg/d and 12 mg/kg/d respectively, ranging from 2 to 24 mg/kg/d. These data show that the therapeutic dose of TPM varies significanty from one patient to the other and indicates that the dose of TPM should indeed be titrated to effect. The clearance of TPM is 44% higher in children

and adolescents than in adults in the absence of enzyme inducing drugs, and 54% higher in the presence of such drugs (Glauser *et al*., 1999 ; Rosenfeld *et al*., 1999). Therefore, steadystate plasma concentrations of TPM are 33% lower in children than in adults.

The frequency of adverse effects reported in our study was higher than reported in previous studies (Glauser, 1999 ; Moreland *et al*., 1999 ; Uldall and Buchholt, 1999). Most of the adverse effects were related to the central nervous system and were relatively mild. None of the children in our study group discontinued treatment because of side effects. It is important to note that adverse effects were seen more frequently in bad responders (Fig 1). The higher incidence of adverse effects in our study, might be explained by the higher starting dose we used than recently has been advised (Glauser, 1999). A starting dose of 0,5-1 mg/kg/d, with increases of 0,5-1 mg/kg/d every 1-2 weeks can probably reduce the incidence of adverse effects.

An increased frequency of valproate-induced hyperammonemic encephalopathy in the presence of TPM has been reported in adults (Hamer *et al*., 2000). Hopefully, this will remain the exception because the results in this series show that valproate and TPM could be an effective combination. Fifty seven percent of the patients in whom one or more concomitant anti-epileptic drugs could be stopped without subsequent increase in seizure rate were kept on a combination of valproate and TPM.

## Conclusion

TPM as adjunctive therapy is a promising drug in children with intractable childhood epilepsy, especially in the patients with West syndrome.

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