Epilepsy & Behavior 112 (2020) 107472

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Behavioral alterations associated with levetiracetam in pediatric epilepsy

Camila Cortes [a,b], Carla Manterola [a,c,*]

[a] Facultad de Medicina Universidad de Chile, Hospital Dr. Luis Calvo Mackenna, Chile
[b] Servicio Pediatría. Hospital de Carabineros, Chile
[c] Servicio de Neuropediatría, Departamento de Pediatría, Clínica Alemana de Santiago, Facultad de Medicina Clinica Alemana, Universidad del Desarrollo, Santiago, Chile

ARTICLE INFO

Article history:
Received 17 July 2020
Revised 4 September 2020
Accepted 6 September 2020
Available online 25 September 2020

Keywords:
Epilepsy
Pediatric
Levetiracetam
Behavior
Adverse effects

ABSTRACT

Levetiracetam (LEV) has an improved pharmacological profile and is one of the most commonly used antiepileptic drugs (AEDs). However, associations between this pharmacological profile and behavioral side effects have been extensively reported in pediatric populations. We assessed behavioral changes after initiation of LEV, prescribed by the treating neurologist, in Chilean patients with epilepsy aged 4–15 years. A behavioral questionnaire was applied at baseline and at two, four, and twelve weeks of treatment. Thirty patients were enrolled: 16 males, 14 females, average age 8 years (range: 4–14). By week four, 23.3% of patients showed significant behavioral alterations that persisted throughout the observation period. No significant alterations emerged after four weeks in the remaining patients. Family history of psychiatric disease and prior behavioral difficulties were predisposing factors for adverse behavioral effects.

Although previous studies associated adverse behavioral effects with LEV in pediatric patients with epilepsy, we believe that this is the first study to use a prospective methodology and standardized tools to quantify the symptomatology. Adverse behavioral effects may significantly affect quality of life for patients and families, diminishing the tolerability of treatment. To ensure successful therapy and improve medical decision-making, it is essential to consider predisposing factors for drug-related adverse effects and to regularly assess for behavioral alterations during treatment.

1. Introduction

Levetiracetam (LEV) is a new-generation antiepileptic drug (AED), approved for adults since 2000 and pediatric patients since 2005 [1]. The drug has an improved pharmacological profile compared with others AED, a wide spectrum of action, high bioavailability, broad therapeutic concentration levels, few pharmacological interactions, linear kinetics, minimal hepatic metabolism, low protein binding, and reversible adverse effects [2]. Levetiracetam is commonly used as monotherapy in pediatric patients with focal or generalized epilepsy [3]. Over the past decade, the frequency of LEV prescriptions has increased significantly, making the drug one of the most commonly prescribed AED today [4,5]. Although adverse behavioral effects of LEV have been extensively reported, these issues are usually considered minimal and manageable. In addition to adverse behavioral effects of AED, epilepsy itself is highly comorbid with psychological symptoms in pediatric population [5,6]. Behavioral and cognitive symptomatology may significantly impact quality of life and decrease AED tolerability in children with epilepsy [7]. These adverse effects must be taken into account in treatment decision-making.

Several second- and third-generation AEDs have become available over the past decades, offering a wider repertoire for pharmacologic epilepsy treatment. Newer drugs have similar seizure-control rates but safer profiles [8]. In 2016, an International League Against Epilepsy (ILAE) task force developed AED recommendations for pediatric patients that included a discussion of adverse cognitive and behavioral effects. The ILAE report noted that LEV may produce positive effects in cognitive areas but negative behavioral outcomes [9]. In a key study, Chen et al. retrospectively assessed nearly 1000 pediatric patients with epilepsy, treated with different AEDs, for adverse psychiatric effects. The authors found that 14% of patients had adverse cognitive or behavioral effects, triggering a reduced dosage in 11% and suspension of the AED in 5% of patients [9]. Of all AED studied, LEV showed the highest rate of adverse psychiatric effects, with a reported range of 4–88% [10,11]. Some of the adverse behavioral effects that have been described include irritability, aggressivity, hostility, emotional lability, abnormal conduct, hyperactivity, mood disorder, fatigue, somnolence, and suicide attempts [12–18]. The physiopathological mechanism underlying adverse behavioral effects related to LEV is not fully understood. Some findings suggest that there is a relationship between negative modulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and reduced serotine levels [19]. Predisposing factors associated with higher rates of adverse psychiatric effects include AED dosage, age younger than four years, previous psychiatric disease, generalized

* Corresponding author at: Antonio Varas 360, Providencia, Santiago, Chile.
E-mail addresses: carlamanterolam@gmail.com, cmanterola@uchile.cl (C. Manterola).

https://doi.org/10.1016/j.yebeh.2020.107472
1525-5050/

epilepsy, and frontal lobe epilepsy [8,16,17,20]. Understanding the mechanisms underlying LEV-related behavioral effects, a better characterization of adverse behavioral effects, and an increased knowledge of predisposing factors will lead to improved decision-making regarding LEV prescription and reduced rates of adverse effects.

The *Strengths and Difficulties Questionnaire* (SDQ) is a brief instrument that evaluates conduct in pediatric patients. The tool is based on the *Diagnostic and Statistical Manual of Mental Disorders IV* symptomatology and assesses the behavior, emotions, and interpersonal relationships of children and adolescents. The measure consists of a series of indicators that represent strengths and difficulties, classified into five domains: conduct problems, emotional symptoms, hyperactivity, difficulties in relationships with peers, and prosocial conduct. Each domain consists of three to five questions, rated on a three-point Likert scale with the following statements: "Not true," "true", and "absolutely true" [21]. The instrument may be completed by the caregiver or patient, and the application time is approximately 5 min. The SDQ has been translated into Spanish (SQD-cas) and validated for the Chilean population [21]. The total and domain scores have cutoff points for outcomes characterizing behavior as "normal" or "abnormal." This instrument has been found to be reliable and internally consistent, with a Cronbach's alpha of 0.80 [22]. Furthermore, its low cost and ease of application make this instrument useful for screening behavioral and emotional symptomatology in pediatric populations.

Studies of adverse behavioral effects related to the use of AED in pediatric populations are limited as compared with research on adult patients. A better understanding of how LEV might be related to adverse psychiatric effects that seriously affect patient and family quality of life is essential for improving decision-making around AED prescription. Adverse psychiatric effects must be evaluated with standardized instruments that assess specific areas of symptomatology, and predisposing factors for these side effects should be identified. Our study aimed to evaluate changes in behavior after initiation of LEV treatment, using the SDQ-cas in Chilean patients with epilepsy aged 4–15 years. Frequency, characterization, and associated factors of adverse behavioral effects will be analyzed.

2. Materials and methods

2.1. Participants

A convenience sample was selected from ambulatory and hospitalized patients evaluated by the Pediatric Neurology Department at Dr. Luis Calvo Mackenna Hospital in Santiago, Chile between 2017 and 2018. Dr. Luis Calvo Mackenna Hospital is a tertiary institution that cares for patients from an extensive area of the city. Patients aged 4–15 years old with a diagnosis of epilepsy who were prescribed LEV by their treating physician were selected. Levetiracetam may be used as mono- or polytherapy. Patients with any of the following characteristics were excluded: a) initiation of another AED within 4 months of study entry, b) history of adverse behavioral effects with another AED, and c) caregivers incapable of responding to the questionnaire. If the patient reported adverse behavioral effects, he/she was referred for evaluation by the treating pediatric neurologist. All patients provided assent for participation, and written consent was provided by caregivers.

2.2. Measures

Demographic, medical, and diagnostic information was obtained from anamnesis, clinical evaluation, and medical charts. Data included age, sex, clinical evaluations of psychomotor development or cognitive capacity, personal and family history of psychiatric disease, nonpsychiatric comorbidities, behavioral difficulties, type of epilepsy, electroencephalographic studies, use of other AEDs, and LEV dosage. The SDQ-cas was given to caregivers immediately prior to initiating LEV and after 2, 4, and 12 weeks of treatment. The questionnaire was administered by a researcher during a medical visit or by phone. Treatment adherence was reported by caregivers.

2.3. Statistical analysis

A database was created and analyzed using STATA statistical software (Stata/IC 15) for Windows. Frequencies and percentages were used to summarize the categorical data, and continuous data were summarized using means and standard deviations (SD). Data analysis was performed using Fisher's test for categorical variables or a t-test for continuous variables; p-values below 0.05 were considered statistically significant. Patients who discontinue treatment with LEV will be included for the period receiving treatment.

2.4. Ethics

The study was approved by the local Ethics Committee of the Universidad de Chile School of Medicine.

3. Results

3.1. Patient characteristics (Table 1)

A total of 30 children (16 males and 14 females) were enrolled in this study. The mean patient age was 8 years (SD 3.3; range 4 to 14). Ten patients presented with clinically abnormal development, characterized as a global developmental delay in four and a language delay in six of the patients. Moreover, 40% of patients had a family history of psychiatric disease; 63% had a nonpsychiatric comorbidity; 10% had a psychiatric comorbidity, all of them diagnosed with attention-deficit hyperactivity disorder (ADHD); and 30% reported previous behavioral problems at home or school. Fifteen (50%) patients were diagnosed with focal epilepsy, and the other half with generalized epilepsy. The etiological cause of the epilepsy was not established in the majority of the patients at study enrollment. At the time when LEV was initiated, 70% of patients had abnormal electroencephalographic results; 19 (63%) showed interictal epileptiform activity (5/19 temporal, 4/19 central–temporal, 3/19 central–frontal, 3/19 multifocal, 2/19 frontal, and 2/19 generalized), and slow background activity was found in 2 (7%) patients. A total of 24 (80%) patients used LEV as monotherapy, while 6 (20%) used LEV in polytherapy. Of these six, 5/6 used two AEDs; other AEDs prescribed included phenobarbital, phenytoin, valproic acid, and clobazam. One patient had a three-AED regimen of LEV, clobazam, and

Table 1
Demographic and clinical characteristics (total = 30).

Characteristic	n	%
Age, mean (range)	8.03 (4–14) years	
Sex		
Male	16	53.3
Female	14	46.7
Normal psychomotor development	20	66.7
Psychiatric comorbidity	3	10
Nonpsychiatric comorbidity	19	63.3
History of behavioral difficulties at home	8	26.7
History of behavioral difficulties at school	3	10
Family history of psychiatric disease	12	40
Type of epilepsy		
Focal	15	50
Generalized	15	50
Pretreatment EEG findings		
Normal	9	30
Abnormal	21	70
Interictal epileptiform activity	19	63.3
Slow background activity	2	6.7
Concomitant AEDs	6	20
Daily LEV dosage, mean (range)	32 (20–66) mg/kg/day	

EEG: electroencephalography, AED: antiepileptic drug, LVT: levetiracetam.

valproic acid. The mean LEV dose was 32 (SD: ±9.72; range: 20–66) mg/k/day. Levetiracetam starting dose and speed of titration was not included as a study variable. All patients' caregivers reported pharmacological adherence.

3.2. Frequency of adverse behavioral effects after LEV initiation

The SDQ-cas was applied to every patient immediately before initiation of LEV treatment. At baseline, 29 (97%) scored within normal range according to the norms for the questionnaire, with an average score of 5.8 points (±4.1). Only one patient, previously diagnosed with ADHD, was classified as showing "abnormal" behavior, primarily attributable to the hyperactivity domain. At week two of treatment, the median score was 8.6 (±5.3), with three (10%) of patients moving from the "normal" to "abnormal" SQD-cas behavior category. By week four, seven (23.3%) patients were classified as having "abnormal" behavior according to SQD-cas score. These behavioral abnormalities persisted through week twelve of follow-up. No patient classified as having "normal" behavior at week four moved into the "abnormal" behavior category when evaluated at week twelve. Six patients discontinued LEV between weeks four and twelve, four due to insufficient seizure control and two due to adverse behavioral effects. Children who maintained "normal" behavior according to the SQD-cas showed small variations in score throughout the study. Behavioral outcomes according to SDQ-cas score at baseline and weeks two, four, and twelve of LEV treatment are presented in Fig. 1. Individual SDQ-cas scores at all timepoints and the threshold dividing "normal" and "abnormal" behavior are shown in Fig. 2.

3.3. Characterization of adverse behavioral effects

Patients with adverse behavioral effects after initiation of LEV showed effects in all domains measured by the SDQ-cas, with exception of the prosocial domain. Conduct problems, emotional symptoms, and hyperactivity were the most significantly affected domains. Changes in domain scores between baseline and week four for patients with adverse behavioral effects are shown in Fig. 3.

3.4. Demographic and clinical factors associated with adverse behavioral effects

Patients were classified as with or without adverse behavioral effects after four weeks of LEV treatment. Demographic and clinical factors associated with the presence of adverse effects were studied. Significant differences in the appearance of adverse behavioral effects were related to previous behavioral difficulties at school or home and family history of psychiatric disease. No differences were found for normal/abnormal development, nonpsychiatric comorbidities, absence/presence of previous psychiatric pathology, mono/polytherapy, normal/abnormal electroencephalographic results, or LEV dosage. Statistical significance was stated for p values below 0.05 and 28 degrees of freedom using Fisher's test. A comparison of the demographic and clinical characteristics of patients with and without adverse behavioral effects is shown in Table 2.

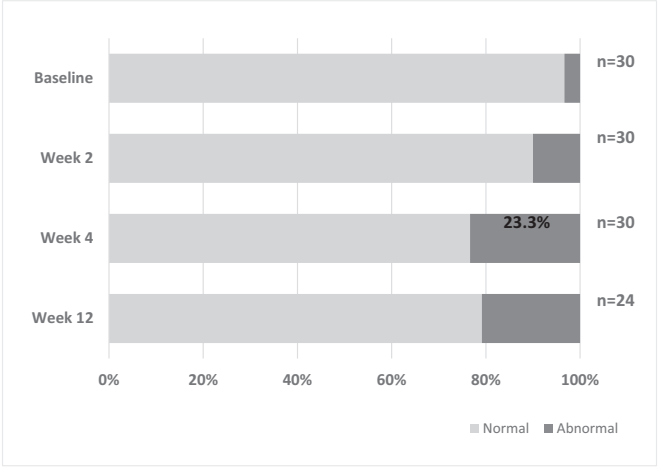

Fig. 1. Behavioral outcome according to SDQ-cas score at baseline and weeks two, four, and twelve of treatment with levetiracetam. SDQ-cas scores after before and during treatment with levetiracetam.

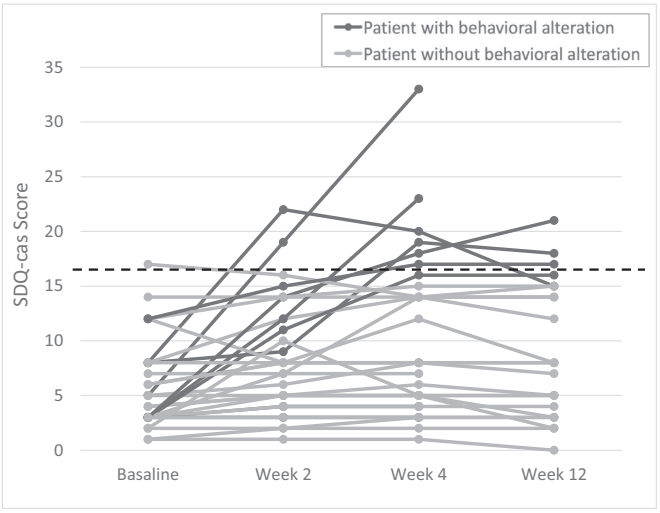

Fig. 2. Individual SDQ-cas scores at baseline and weeks two, four and twelve of treatment with levetiracetam. Individual SDQ-cas scores before and during treatment with levetiracetam. Dashed line indicates threshold dividing "normal" from "abnormal" conduct.

4. Discussion

Levetiracetam is a broad-spectrum AED with an improved pharmacological profile, but adverse behavioral effects in adult and pediatric population have been extensively reported. The present study supports these reports by demonstrating the association using a prospective methodology and standardized behavioral measurements. We showed that after initiation of LEV, 23% of patients showed behavioral difficulties not evident before the pharmacologic treatment. The SDQ-cas was used to obtain objective measurements of various behavioral dimensions and to quantify changes during the follow-up period. Most patients showed no adverse behavioral effects, remaining in the "normal" SDQ-cas behavioral category, but also showed no improvement on any of the dimensions evaluated. Nearly a quarter of the patients had a shift in their behavioral SQD-cas classification outcome from "normal" to "abnormal." Behavioral changes present during the first four weeks of treatment maintain through the study time. Patients with adverse behavioral effects had a similar profile of behavioral changes. Hyperactivity, conduct, and emotional difficulties were the domains with the most marked changes. It is important to characterize the specific behavioral symptomatology associated with adverse effects of LEV. An exhaustive symptomatologic characterization will allow physicians to direct their clinical evaluation and anticipate eventual changes to caregivers. Moreover, this knowledge will facilitate accurate clinical evaluation, helping professionals to identify or exclude other pathologies, related or unrelated to epilepsy, that may present as behavioral difficulties.

Understanding potential adverse behavioral effects of LEV is important when making treatment decisions in pediatric epilepsy. Our results show that adverse behavioral effects are significantly more common in patients with a history of behavioral difficulties at home or school, but prior history of a psychiatric comorbidity was not a significant predisposing factor. It is important to evaluate the behavior of the child during

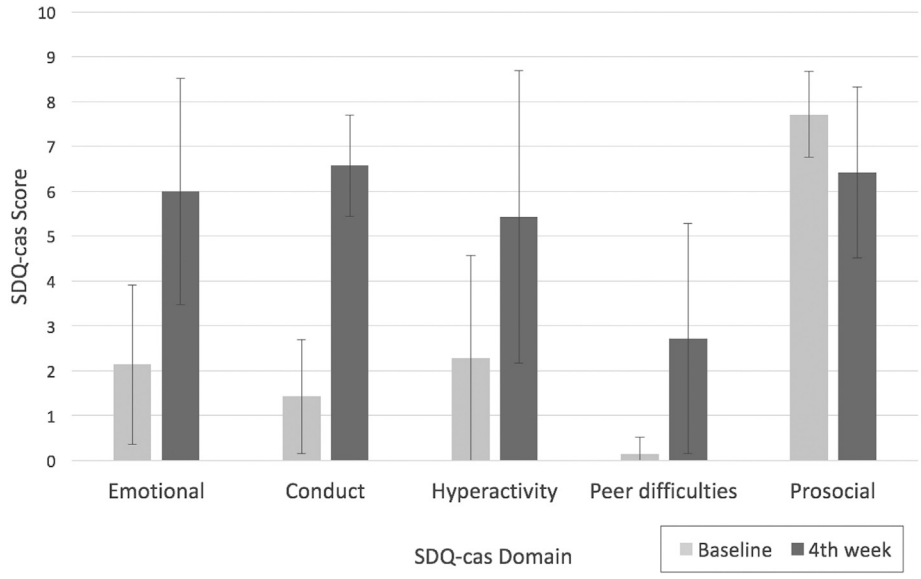

Fig. 3. SDQ-cas domain scores at baseline and week four of treatment in patients with abnormal behavior after initiation of levetiracetam. Variations in SDQ-cas scores by domain in patients with behavioral alterations.

clinical consults and to complement these observations with reports from the caregivers and school to optimize characterization of baseline behavior. Children with a history of behavioral difficulties, even when these issues are not formally diagnosed as a disorder, are at higher risk of adverse behavioral effects when treated with LEV. Family medical history of psychiatric disease is another variable that must be taken into account when selecting LEV as an AED. The presence of a developmental delay or cognitive impairment, nonpsychiatric comorbidities, and the use of polytherapy, variables previously described as predicting factors for adverse behavioral effects in patients treated with LEV, were not significant in our study. These differences may be related to the small sample size.

Seven patients in the study shifted from "normal" to "abnormal" behavior after initiation of treatment with LEV as assessed by a standardized tool (SDQ-cas). However, LEV was discontinued in only two of these patients. The standardized instrument used may overdiagnose behavioral difficulties; however, we encourage physicians to carefully evaluate various behavioral domains in patients receiving LEV. Behavioral symptomatology that does not reach the threshold for a pathological diagnosis may nevertheless cause important distress to the family system and affect quality of life.

This study evaluates changes in patient behavior after initiation of LEV as compared with a baseline score. An important limitation of this study is that these changes may be related to other variables. The epilepsy diagnosis, parental stress due to the illness, a history of hospitalizations, pharmacological adherence, and exposure to a structural questionnaire regarding behavior are confounding factors that may have affected the caregiver evaluation. Caregivers of patients with previous behavioral difficulties and have family history of psychiatric disease may have an observation bias when exposed to a questionnaire. Levetiracetam starting dose and titration speed had been associated with behavioral adverse effects; these variables were not included in our analysis and may be a confounder. Furthermore, our study was performed in a tertiary hospital, and therefore, most of the patients had other medical pathologies, which may constitute a selection bias. We were not able to compare different types of epilepsy in relationship with LEV-related adverse effects. The sample size was too small for such an analysis; furthermore, the etiology of the disorder was unknown in most patients at the time of enrollment. These disease-related factors have been reported as significantly related to the presence of adverse effects. Finally, the objective of this study was to observe changes in behavior during the first three months of treatment with LEV; therefore, emergence of new issues or persistence of symptoms past this timepoint was not studied.

Various studies have reported adverse behavioral effects related to treatment with LEV in pediatric populations. Our results support previous findings using a prospective methodology and a standardized and validated measurement of behavior. Levetiracetam is an AED that is widely used as it shows favorable pharmacokinetic properties, treats a broad spectrum of epilepsy disorders, and rarely causes severe adverse effects. When selecting an AED, physicians must balance the probability of seizure control and the probability of adverse effects. Adverse

Table 2
Predisposing factors associated with adverse behavioral effects.

Variable	Patients with behavioral alterations (total = 7)		Patients without behavioral alterations (total = 23)		p-Value
	n	%	n	%	
Abnormal development	2	28.5	8	34.9	0.4865
Psychiatric comorbidity	1	14.3	2	8.7	0.5769
Nonpsychiatric comorbidity	6	85.7	13	56.5	0.0819
History of behavioral difficulties at home	5	71.4	3	13	0.0467*
History of behavioral difficulties at school	3	42.8	0	0	0.0048*
Family history of psychiatric disease	6	85.7	6	26.1	0.0149*
Concomitant AEDs	2	28.5	4	17.4	0.2738

AED: antiepileptic drug.
* Statistical significance: $p > 0.05$.

behavioral effects may diminish quality of life for patients and caregivers. Evaluating individual predisposing factors for adverse behavioral effects and actively assessing for behavioral changes will result in better medical decision-making.

5. Conclusion

The present study found adverse behavioral effects in one quarter of a sample of pediatric patients treated with LEV. To the best of our knowledge, this is the first study that demonstrates this association prospectively using a standardized instrument to measure conduct and characterize the behavioral dimensions affected. Levetiracetam has proven to be an excellent AED, but physicians must take into account predisposing factors for adverse behavioral effects when considering this prescription, and behavioral changes should be evaluated regularly during treatment.

Declaration of competing interest

None of the authors have conflicts of interest to disclose.

Acknowledgments

We would like to thank our patients and their caregivers who generously shared their experiences, making this study possible.

References

[1] Lee YJ, Kang H-C, Kim HD, Lee JS. Efficacy and safety of adjunctive levetiracetam therapy in pediatric intractable epilepsy. Pediatr Neurol. 2010;42:86–92. https://doi.org/10.1016/j.pediatrneurol.2009.08.002.
[2] Wright C, Downing J, Mungall D, Khan O, Williams A, Fonkem E, et al. Clinical pharmacology and pharmacokinetics of levetiracetam. Front Neurol. 2013;4:192. https://doi.org/10.3389/fneur.2013.00192.
[3] Ríos-Pohl L. Levetiracetam: Fármaco de amplio espectro y alta seguridad. En: Targas Yacubian E, Contreras-Caicedo G, Ríos-Pohl L, editores. Tratamiento Farmacológico de las Epilepsias, Sao Paulo:Leitura Médica Ltda; 2014, p. 193–8.
[4] Egunsola O, Choonara I, Sammons H. Safety of levetiracetam in paediatrics: a systematic review. PLoS One. 2016;11:1–15. https://doi.org/10.1371/journal.pone.0149686.
[5] Josephson C, Engbers J, Jatte N, Patten S, Marshall D, Lowerison M, et al. Prescription trends and psychiatric symptoms following first receipt of one of several common antiepileptic drugs in general practice. Epilepsy Behav. 2018;84:49–55. https://doi.org/10.1016/j.yebeh.2018.04.012.
[6] Guilfoyle S, Follansbee-Junger K, Smith A, Combs A, Ollier S, Hater B, et al. Antiepileptic drug behavioral side effects and baseline hyperactivity in children and adolescents with new onset epilepsy. Epilepsia. 2018;59:146–54. https://doi.org/10.1111/epi.13946.
[7] Ronen G, Rosembaum P, Boyle M, Streiner D. Patient-reported quality of life and biopsychosocialhealth outcomes in pediatric epilepsy: an update for healthcare providers. Epilepsy Behav. 2018;86:19–24. https://doi.org/10.1016/j.yebeh.2018.05.009.
[8] Moavero R, Santarone M, Galasso C, Curatolo P. Cognitive and behavioral effects of new antiepileptic drugs in pediatric epilepsy. Brain Dev. 2017;39:464–9. https://doi.org/10.1016/j.braindev.2017.01.006.
[9] Aldenkamp A, Besag F, Gobbi G, Caplan R, Dunn DW, Sillanpää M. Psychiatric and behavioural disorders in children with epilepsy (ILAE task force report): adverse cognitive and behavioural effects of antiepileptic drugs in children. Epileptic Disord. 2016;18:555–67. https://doi.org/10.1684/epd.2016.0817.
[10] Chen B, Detyniecki K, Choi H, Hirsch L, Katz A, Legge A, et al. Psychiatric and behavioral side effects of anti-epileptic drugs in adolescents and children with epilepsy. Eur J Paediatr Neurol. 2017;21:441–9. https://doi.org/10.1016/j.ejpn.2017.02.003.
[11] Wheless JW. Levetiracetam in the treatment of childhood epilepsy. Neuropsychiatr Dis Treat. 2007;3:409–21.
[12] Shukla G, Gupta A, Agarwal P, Poornima S. Behavioral effects and somnolence due to levetiracetam versus oxcarbacepina a retrospective comparasion study of north Indian patients with refractory epilepsy. Epilepsy Behav. 2016;64:216–8. https://doi.org/10.1016/j.yebeh.2016.08.005.
[13] Levisohn P, Mintz M, Hunter S, Yang H, Jones J. Neurocognitive effects of adjunctive levetiracetam in children with partial-onset seizures: a randomized, double-blind, placebo-controlled, noninferiority trial. Epilepsia. 2009;50:2377–89. https://doi.org/10.1111/j.1528-1167.2009.02197.x.
[14] Verrotti A, Prezioso G, Di Sabatino F, Franco V, Chiarelli F, Zaccara G. The adverse event profile of levetiracetam: a meta-analysis on children and adults. Seizure. 2015;31:49–55. https://doi.org/10.1016/j.seizure.2015.07.004.
[15] Feng XF, Chen YX, Liu L, Xiao N. Retention rates of levetiracetam in Chinese children and adolescents with epilepsy. Eur J Paediatr Neurol. 2014;19:143–8. https://doi.org/10.1016/j.ejpn.2014.11.001.
[16] Tekgül H, Gencpinar P, Çavusoglu D, Dündar NO. The efficacy, tolerability and safety of levetiracetam therapy in a pediatric population. Seizure. 2016;36:16–21. https://doi.org/10.1016/j.seizure.2016.01.017.
[17] Mbizvo G, Dixon P, Hutton JL, Marson AG. The adverse effects profile of levetiracetam in epilepsy: a more detailed look. Int J Neurosci. 2014;124:627–34. https://doi.org/10.3109/00207454.2013.866951.
[18] Halma E, De Louw AJ, Klinkenberg S, Aldenkamp AP, Ijff DM, Majoie M. Behavioral side-effects of levetiracetam in children with epilepsy: a systematic review. Seizure. 2014;23:685–91. https://doi.org/10.1016/j.seizure.2014.06.004.
[19] Hansen C, Ljung H, Brodtkorb E, Reimers A. Mechanisms underlying aggressive behavior induced by antiepileptic drugs: focus on topiramate, levetiracetam and perampanel. Behav Neurol. 2018;2018:2064027. https://doi.org/10.1155/2018/2064027.
[20] Verotti A, D'Adammo E, Parisi P, Chiarelli F, Curatolo P. Levetiracetam in childhood epilepsy. Paediatr Drugs. 2010;12:177–86. https://doi.org/10.2165/11316250-000000000-00000.
[21] Brown P, Capella C, Antivilo A. Propiedades psicométricas de la versión para padres del Strengths and difficulties questionnaire. Revista de Psicología-Universidad de Chile. 2014;23(2):28–44.
[22] Stone LL, Otten R, Engels RC, Vermulst AA, Janssens JM. Psychometric properties of the parent and teacher versions of the Strengths and Difficulties Questionnaire for 4 to 12 years olds: a review. Clin Child Fam Psychol Rev. 2010;13:254–74. https://doi.org/10.1007/s10567-010-0071-2.