

Valproate-induced enuresis: a prospective study

WISSAM R YAMAK¹ | GHASSAN HMAIMESS² | YAMANE MAKKE¹ | SANDRA SABBAGH³ | MAHER ARABI⁴ | AHMAD BEYDOUN¹ | WASSIM NASREDDINE¹

1 Department of Neurology, American University of Beirut Medical Center, Beirut; **2** Department of Pediatrics, Saint George Hospital University Medical Center, University of Balamand, Beirut; **3** Department of Pediatrics, Hotel Dieu de France Hospital, Beirut, Lebanon; **4** Department of Neurology, Ibn Sina Hospital, Kuwait.

Correspondence to Wassim Nasreddine at American University of Beirut Medical Center, PO Box 11-0236, Riad El-Solh 1107 2020 Beirut, Lebanon. E-mail: wn13@aub.edu.lb

PUBLICATION DATA

Accepted for publication 28th January 2015.

Published online 25th March 2015.

AIM The aim of this study was to determine the frequency and characteristics of secondary enuresis in children initiated on valproate treatment.

METHOD This was a prospective study conducted in children aged 5 to 12 years with suspected newly diagnosed epilepsy and maintained on valproate for at least 1 month. Adverse events spontaneously reported by parents were recorded at each follow-up visit. In addition, we specifically asked about enuresis and other side effects known to occur with valproate treatment. We assessed the frequency of enuresis and its association with a number of variables.

RESULTS Seventy-two children (43 males and 29 females) with a mean age of 8 years 7 months (range 5–12y) were included in this study. Secondary enuresis developed in 17 (24%) of these children after, on average, 19.8 days of exposure to valproate. The data obtained from a multivariate analysis indicate that age was the only significant factor in predicting the development of enuresis. Enuresis ceased in all children after discontinuation of valproate use, and in 10 out of 11 children still on the drug.

INTERPRETATION Secondary enuresis is a common adverse event associated with valproate use in children, which is not usually spontaneously reported and is reversible in most cases.

Valproate is a broad-spectrum antiepileptic drug approved as monotherapy and adjunctive therapy for the treatment of simple and complex partial seizures in adults and children 10 years or older; as adjunctive therapy for the treatment of multiple seizure types, including absence seizures; for the treatment of acute manic episodes in those with bipolar disorder older than 18 years of age; and as a prophylactic agent for migraine headaches in adults and children older than 16 years.¹ Adverse events associated with valproate include idiosyncratic reactions, such as hepatotoxicity and pancreatitis, and dose-related adverse events including weight gain, hair thinning, tremor, drowsiness, nausea, vomiting, ataxia, and thrombocytopenia.^{2–4}

Primary and secondary nocturnal enuresis is common in children, with a peak prevalence of 15% to 25% at age 5 years.⁵ Although enuresis typically disappears as the child matures, it can be distressing for children and their families and can prompt treatment with desmopressin or imipramine, or behavioural interventions.^{5,6}

An association between the emergence of enuresis and treatment with valproate has been suggested but is not well characterized in the literature.^{7–11} A recently published review, which comprehensively described the adverse events of valproate, failed to mention enuresis as a side effect of this drug.¹²

In this study, we prospectively assessed the frequency of enuresis in children with suspected newly diagnosed epilepsy, naive to antiepileptic drug treatment, and initiated on valproate. We also attempted to elucidate the characteristics of and the risk factors for the development of valproate-induced enuresis.

METHOD

Children eligible for this study were identified from those already enrolled in an ongoing prospective study, which started more than 3 years ago, in children and adults with suspected newly diagnosed epilepsy. Adult and paediatric neurologists from across Lebanon refer patients with newly diagnosed suspected seizures/epilepsy to the American University of Beirut Medical Center, where a full neurological evaluation, 3-hour sleep-deprived video-electroencephalography, and epilepsy protocol brain magnetic resonance imaging are performed. For each patient, the results of this workup are conveyed to the referring physician, who then decides whether or not to initiate treatment and, if so, which antiepileptic drug to use. Patients were subsequently evaluated every 3 months during the first year and every 6 months thereafter, with additional visits as needed based on seizure recurrence or adverse events.

Definition of nocturnal enuresis

For a diagnosis of nocturnal enuresis, a child between 5 and 6 years old should have two or more bedwetting episodes per month, and a child of older than 6 years of age should have one or more bedwetting episodes per month. Primary nocturnal enuresis was diagnosed when a child did not achieve any periods of night-time dryness over a period of 6 consecutive months. For the purpose of this study, we used the International Children's Continence Society definition of secondary nocturnal enuresis, which was considered present when a child had a period of night-time dryness for at least six consecutive months but then relapsed.¹³

Inclusion criteria

We included all children within the age range 5 to 12 years evaluated over a 2-year period (October 2010–October 2012), and who were initiated and maintained on valproate for at least 1 month and attended at least one follow-up appointment. Children with psychomotor delay who required nappies and those with primary enuresis were excluded.

Assessment of enuresis

At the follow-up visit, parents were initially asked about seizure control and each child's seizure diary was reviewed. In addition, the spontaneously reported adverse events associated with valproate were recorded. Subsequently, parents were specifically asked about the occurrence of nocturnal enuresis and its frequency (d/mo). In addition, parents were specifically queried about the occurrence of the following adverse events commonly associated with valproate: tremor, dizziness, drowsiness, ataxia, headache, irritability, nausea, vomiting, anorexia, diarrhoea, hair loss, increased appetite, and weight gain.

For children who developed enuresis, we recorded the time from the initiation of valproate treatment to the onset of enuresis, the dose of valproate (mg/kg/d) at enuresis onset, and the weight of the child at initiation of valproate and at the time of follow-up. At follow-up visits, the time to resolution of enuresis (whether spontaneous or after discontinuation of valproate) was ascertained, and the duration of treatment with valproate was calculated.

Ethical approval

This study was approved by the Institutional Review Board of the American University of Beirut Medical Center and all children enrolled in this study provided an informed consent form signed by one of their parents.

Statistical analysis

For continuous variables, descriptive statistics (mean, median, range, and frequencies) with percentages were calculated. Statistical analyses were performed using χ^2 tests for categorical variables, and Student's *t*-tests for continuous variables.

What this paper adds

- Enuresis is a common adverse event of valproate exposure in children.
- Enuresis rapidly resolves in all children after discontinuation of valproate.
- Enuresis also resolves eventually in the vast majority of children maintained on valproate.
- Physicians should specifically inquire about this valproate-induced adverse event.

A univariate binary logistic regression analysis was performed with 'the occurrence of enuresis' as the dependent variable and each of the following continuous independent variables: age, weight, change in weight (%), duration of treatment with valproate, and maintenance daily dose of valproate. The multivariate analysis was performed using stepwise forward multivariate logistic regression analysis. We included the following independent variables in the model: age, weight, change in weight (%), duration of treatment with valproate, and maintenance daily dose of valproate. The alpha level for all tests of hypotheses of no effect was set to 0.05.

RESULTS

A total of 96 children aged between 5 and 12 years were initiated on valproate. Of these children, 12 were excluded because they were treated with valproate for <1 month for the following reasons. Eight children were diagnosed with non-epileptic spells resulting in the discontinuation of valproate, two children experienced significant adverse events (irritability, poor concentration, alopecia, and weight gain) leading to withdrawal of the drug, and two children were diagnosed with a maturational epilepsy; one of them was switched to carbamazepine by his treating physician; in the other, treatment was discontinued. Twelve additional children were excluded: seven failed to attend a follow-up visit, two had severe developmental delay and were using nappies, and three had primary nocturnal enuresis.

The remaining 72 children (43 males and 29 females, mean age 8y 7mo, range 5–12y) were included in this study and initiated on valproate (mean dose 13.6mg/kg/d). The type of valproate used and the titration schedule were at the discretion of the referring physician. In general, children were initiated on slow-release formulation tablets if they were able to swallow pills or on a liquid valproate formulation otherwise. Although the titration schedule was not uniform, the maintenance dose was reached within 16 days for all children.

Sixty-eight (94%) of the participants had epilepsy, one experienced a single unprovoked seizure, one experienced an acute symptomatic seizure, and two children presented with paroxysmal spells, the nature of which has not yet been fully elucidated. Of the 68 children with epilepsy, idiopathic generalized epilepsy was diagnosed in 23, idiopathic focal epilepsy in 18, and symptomatic focal epilepsy in the remaining 27. The results of physical and neurological examinations were normal for all of these children.

Children with enuresis

Seventeen (10 males and 7 females) of the 72 children developed secondary enuresis after exposure to valproate. None of these children experienced diurnal urinary incontinence. This adverse event was spontaneously reported by parents in only three instances (4%), while the remaining 14 instances were reported only when parents were asked directly. Children who developed secondary enuresis did so after a mean exposure time to valproate of 19.8 days. The characteristics of children who developed secondary enuresis compared with those who did not are summarized in Table I.

Factors associated with the occurrence of secondary enuresis

In a univariate analysis using binary logistic regression, there was evidence that age and weight were significant in the model for predicting the probability of occurrence of nocturnal enuresis (Table I). In addition, there was evidence of a strong linear correlation between age and weight ($r=0.68$, $p<0.016$). However, a multivariate analysis

suggested that only age could significantly predict the occurrence of enuresis ($p=0.022$).

There is no evidence that maintenance valproate dose (mg/kg/d), weight change (%), or duration of treatment with valproate can predict the occurrence of enuresis.

When the frequency of secondary enuresis was stratified by age (Fig. 1), it was highest for children 8 years old or younger, occurring in 11 out of 30 (37%) children in this age range, compared with only 6 out of 42 (14%) children of more than 8 years of age ($p=0.03$, χ^2).

Course of enuresis

Enuresis resolved in 16 of the 17 children (94%) who developed secondary enuresis. In 10 of these children, it resolved spontaneously while the children were still maintained on valproate, whereas, in the remaining six children, enuresis abated after discontinuation of the drug.

The mean time required for spontaneous resolution of enuresis was 210 days (median 150, range 30–630). The mean ages of the children at the time of emergence of enuresis and at the time of its spontaneous resolution were

Table I: Comparison of variables between children with or without secondary enuresis

	Children with enuresis			Children without enuresis			p^a
	Mean	Median	Range	Mean	Median	Range	
Age (y:mo)	7:6	7:0	5:5–10:8	8:11	9:2	5:0–12:0	0.012
Weight (kg)	25.9	28.3	17–35	34.1	31.7	15.5–70.5	0.006
Initial valproate dose (mg/kg/d) ^b	12.8	12.5	4.7–22.2	13.8	12.5	3.6–27.8	0.6
Maintenance valproate dose (mg/kg/d) ^c	22.4	22.3	8.3–34.1	21.9	20.7	7.3–37.8	0.8
Weight change (%)	1	1	–1 to 2	1	1	–1 to 4	0.13
Duration of valproate therapy (mo)	21.2	24	1–30	19.3	21	1–38	0.44
Dose of valproate (mg/kg/d) at the time of enuresis ^d	21.6	19.8	14.7–34.1				
Time of occurrence of enuresis after initiating valproate (d)	19.8	14	1–60				
Frequency of enuresis (occurrences/mo)	11.9	7	1–30				

^aCalculated using the binary logistic regression model. ^bDaily valproate dose the child was initially started on. ^cDaily valproate dose reached at the end of the titration phase. ^dDaily valproate dose the child was taking at the onset of enuresis.

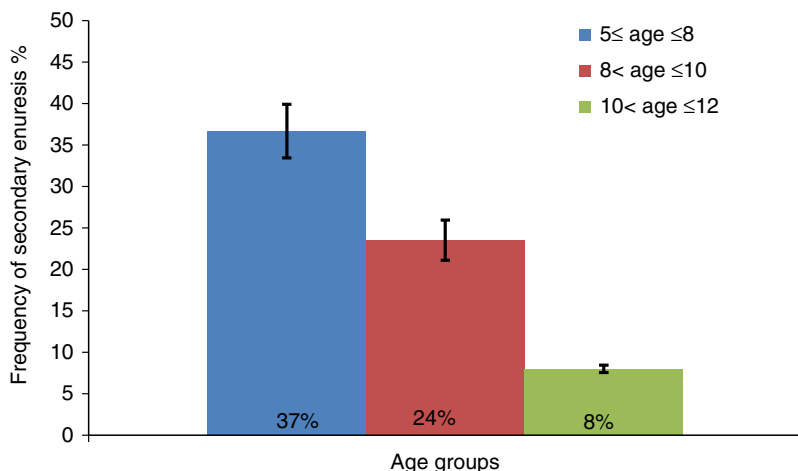


Figure 1: Frequency of secondary enuresis stratified by age group. The vertical lines represent standard errors.

Table II: Other adverse events related to valproate treatment stratified by type and severity

Adverse event (n=72)	Mild (%)	Moderate (%)	Severe (%)
Tremor	4 (6)	0	0
Dizziness	3 (6)	1 (1)	0
Drowsiness	7 (10)	4 (6)	1 (1)
Ataxia	1 (6)	0	0
Headache	3 (4)	0	0
Irritability/nervousness	9 (13)	4 (6)	7 (10)
Nausea	4 (6)	1 (1)	0
Vomiting	2 (3)	1 (1)	1 (1)
Anorexia	0	0	1 (1)
Diarrhoea	0	0	1 (1)
Gastrointestinal distress	4 (6)	1 (1)	0
Alopecia	2 (3)	6 (8)	4 (6)
Increased appetite	14 (19)	14 (19)	10 (14)
Weight gain	14 (19)	8 (11)	7 (10)

7 years 9 months (range 5y 10mo–10y 8mo) and 8 years 4 months (range 6y–10y 11mo), respectively. There was no significant correlation between the frequency of enuresis (d/mo) and the time to its resolution. Similarly, there was no significant correlation between the age of these children and the time to enuresis resolution. Only one child was still experiencing enuresis after 18 months while maintained on valproate.

Enuresis resolved in five of the six children in whom valproate treatment was discontinued after a mean duration of 16.4 days (median 7, range 4–60). The remaining child experienced a gradual improvement of enuresis that eventually abated 10 months after stopping the drug.

In no case was valproate discontinued because of enuresis. It was stopped because of severe irritability in two children, because of seizure remission for 1 to 2 years in three children, and because of lack of efficacy in one child.

Other adverse events

The other adverse events experienced by children while on valproate treatment are tabulated by type and severity (Table II). There were no significant correlations between secondary enuresis and the frequencies of the following specific adverse events: tremor, dizziness, drowsiness, ataxia, headache, irritability/nervousness, nausea, vomiting, anorexia, diarrhoea, gastrointestinal distress, alopecia, increased appetite, or weight gain.

DISCUSSION

This is the first prospective study specifically aimed at defining the frequency and evaluating the characteristics and risk factors associated with the development of secondary nocturnal enuresis in children after exposure to valproate. Our study has established that enuresis is a common adverse event associated with valproate, occurring in approximately 24% of children between the ages of 5 and 12 years treated with this drug.

Some previous studies and case reports evaluating the adverse events associated with valproate mentioned enuresis

as a possible side effect of this drug with a frequency, when reported, ranging between 2% and 7%.^{7–11,14,15} In a retrospective study of 100 children, which evaluated the frequency and amount of weight gain after exposure to valproate, nocturnal enuresis was reported in 7% of participants; however, further details, other than the fact that enuresis spontaneously abated after a few months, were not provided.⁷ In a prospective comparative trial of phenobarbital, primidone, and valproate for the prevention of febrile seizures, 1 child out of 48 children (2%) exposed to valproate was reported to have developed enuresis.⁹ Another study evaluating the adverse event profile of valproate in children with epilepsy mentioned that 5 out of 88 children (6%) developed nocturnal enuresis.⁸

A substantially higher frequency of secondary enuresis was documented in our study, most likely because we specifically inquired about this adverse event. In fact, enuresis was spontaneously reported by the parents of only 3 out of 72 children (4%) in this study, which is within the reported frequency range of these previous studies. Therefore, this emphasizes the importance of paediatricians or paediatric neurologists specifically enquiring about nocturnal enuresis since this adverse event is rarely spontaneously reported.

Unlike our study, these published studies did not evaluate the characteristics of valproate-induced secondary enuresis.^{7–9} Our data strongly support a causal relationship between valproate and enuresis, because of the close temporal relationship between the initiation of valproate treatment and the onset of enuresis. Among those children who developed enuresis, this adverse event started, on average, 20 days after the initiation of valproate treatment. This is consistent with the few published case reports which documented that the onset of enuresis occurs within 2 to 14 days of starting valproate treatment.^{10,15} In addition, the existence of a causal relationship is strengthened by the fact that enuresis stopped, on average, 16 days after valproate discontinuation. In contrast, although enuresis eventually resolved in the vast majority of children still maintained on valproate, this resolution occurred after an average duration of 210 days. The reversibility of enuresis while on valproate suggests the development of tolerance to this adverse event, or an age-related phenomenon. In fact, the mean age of affected children increased from 7 years 8 months at the time of emergence of enuresis to 8 years 4 months at the time of its resolution.

In addition, we established that valproate-induced secondary enuresis is an age-related adverse event, affecting nearly 37% of children aged 8 years or younger but only 14% of children older than 8 years. We also showed that other variables, including daily valproate dose, duration of treatment, and amount of weight gain, were not significantly associated with the occurrence of secondary enuresis. Furthermore, the mean daily dose of valproate was not significantly different among children who developed this adverse event and those who did not, a finding that suggests that the occurrence of secondary enuresis is not dose related. Data from individual case reports suggest that, at

least in some children, nocturnal enuresis is dose related since it was noted only when valproate dose was increased.^{10,14,15}

Drug-induced secondary enuresis is an uncommon adverse event that has mainly been described after treatment with atypical antipsychotics. This class of drugs has been reported to induce secondary enuresis in 21%, 10%, 7%, and 6% of patients aged 15 to 64 years treated with clozapine, olanzapine, quetiapine, and risperidone, respectively.¹⁶ In addition, case reports have documented the occurrence of secondary enuresis in children after initiation of treatment with risperidone.^{17,18}

The mechanism of enuresis is believed to be multifactorial and includes sleep disorders, genetic factors, decreased functional bladder capacity, and the absence of a circadian nocturnal rise in the secretion of the antidiuretic hormone arginine vasopressin.⁵ One sleep disorder associated with enuresis is obstructive sleep apnoea,¹⁹ which can be worsened by weight gain, a known adverse event of valproate treatment.⁷ However, this mechanism for valproate-induced enuresis is unlikely, since we have established that the emergence of enuresis is not associated with weight gain. Another potential aetiology of enuresis is 'deeper sleep' with inability to arouse,^{5,6,20} a sleep architectural change that was reported after valproate intake.^{21,22} One study reported that the percentage of deep sleep increased from 19% to 30% after treatment with valproate,²¹ while

another found that total sleep time significantly decreased after discontinuation of valproate.²² Our study cannot confirm or reject this hypothesis since we did not perform polysomnography on our cohort.

In summary, valproate-induced secondary enuresis is an underreported but frequent adverse event in children, especially in those aged between 5 years and 8 years, is typically not spontaneously reported by parents, and is reversible upon discontinuation of valproate. It is important for clinicians to be aware of this adverse event, since enuresis in children with epilepsy might lead to the suspicion of unwitnessed nocturnal seizures and an unwarranted increase in the dose of valproate or in the addition of another antiepileptic drug. In addition, enuresis can have a psychological impact on children including social avoidance, unhappiness, shame, low self-esteem, and behavioural problems.^{23–25}

ACKNOWLEDGEMENTS

We thank Dr Hani Tamim, Director of the Biostatistics Unit, Clinical Research Institute, American University of Beirut Medical Center, who assisted with the final statistical analysis. The authors have stated that they had no interests that might be perceived as posing a conflict or bias. Funded in part by grants from the Lebanese National Council for Scientific Research (Grant number: LCR 114110 522214) and the American University of Beirut (Grant number: 1131613 52480 115372099990000).

REFERENCES

- US Food and Drug Administration. (2009) Depakote Tablets (divalproex sodium) Tablet (Abbott Laboratories). Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2009/018723s039lbl.pdf (accessed 20 October 2014).
- Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *N Engl J Med* 1992; **327**: 765–71.
- Beydoun A, Sackellares JC, Shu V. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. Depakote Monotherapy for Partial Seizures Study Group. *Neurology* 1997; **48**: 182–8.
- Nasreddine W, Beydoun A. Valproate-induced thrombocytopenia: a prospective monotherapy study. *Epilepsia* 2008; **49**: 438–45.
- Thiedke CC. Nocturnal enuresis. *Am Fam Physician* 2003; **67**: 1499–506.
- Cendron M. Primary nocturnal enuresis: current concepts. *Am Fam Physician* 1999; **59**: 1205–14.
- Egger J, Brett EM. Effects of sodium valproate in 100 children with special reference to weight. *Br Med J* 1981; **283**: 577–81.
- Herranz JL, Arteaga R, Armijo JA. Side effects of sodium valproate in monotherapy controlled by plasma levels: a study in 88 pediatric patients. *Epilepsia* 1982; **23**: 203–14.
- Herranz JL, Armijo JA, Arteaga R. Effectiveness and toxicity of phenobarbital, primidone, and sodium valproate in the prevention of febrile convulsions, controlled by plasma levels. *Epilepsia* 1984; **25**: 89–95.
- Panayiotopoulos CP. Nocturnal enuresis associated with sodium valproate. *Lancet* 1985; **i**: 980–1.
- Zaiem A, Aouinti I, Lakhous G, et al. Secondary nocturnal enuresis associated with valproic acid. *Therapie* 2013; **68**: 59–60.
- Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem* 2013; **46**: 1323–38.
- Nørgaard J, Van Gool J, Hjälmås K, et al. Standardization and definitions in lower urinary tract dysfunction in children. *Br J Urol* 1998; **81**: 1–16.
- Gosavi DD, Suman A, Jain M. Sodium valproate induced increased frequency of micturition and enuresis. *Ind J Pharmacol* 2013; **45**: 87–8.
- Cheng W, Lin X, Lu D. Sodium valproate-induced enuresis in a pediatric bipolar patient. *Neuropsychiatr Dis Treat* 2013; **9**: 1671–2.
- Harrison-Woolrych M, Skegg K, Ashton J, et al. Nocturnal enuresis in patients taking clozapine, risperidone, olanzapine and quetiapine: comparative cohort study. *Br J Psychiatry* 2011; **199**: 140–4.
- Herguner S, Mukaddes NM. Risperidone-induced enuresis in two children with autistic disorder. *J Child Adolesc Psychopharmacol* 2007; **17**: 527–30.
- Cop E, Oner P, Oner O. Risperidone and double incontinence in a child with autism. *J Child Adolesc Psychopharmacol* 2011; **21**: 647–8.
- Brooks LJ, Topol HI. Enuresis in children with sleep apnea. *J Pediatr* 2003; **142**: 515–8.
- Robert M, Averous M, Besset A, et al. Sleep polygraphic studies using cystomanometry in twenty patients with enuresis. *Eur Urol* 1993; **24**: 97–102.
- Ehrenberg BL, Eisensehr I, Corbett KE, et al. Valproate for sleep consolidation in periodic limb movement disorder. *J Clin Psychopharmacol* 2000; **20**: 574–8.
- Schmitt B, Martin F, Critelli H, et al. Effects of valproic acid on sleep in children with epilepsy. *Epilepsia* 2009; **50**: 1860–7.
- Butler RJ. Impact of nocturnal enuresis on children and young people. *Scand J Urol Nephrol* 2001; **35**: 169–76.
- Redsell SA, Collier J. Bedwetting, behaviour and self-esteem: a review of the literature. *Child Care Health Dev* 2001; **27**: 149–62.
- Kanaheswari Y, Poulsaeman V, Chandran V. Self-esteem in 6- to 16-year-olds with monosymptomatic nocturnal enuresis. *J Paediatr Child Health* 2012; **48**: E178–82.