Comparative Effect of Divided Doses of Adult Solid and Liquid Oral Formulations of Antiepileptic Drugs in the Management of Pediatric Epilepsy

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Abstract

Objective: To compare the differences in the efficacy and safety of the commonly prescribed AEDs in the management of epilepsy in children when using divided doses of adult solid oral formulations (DDSF) with the liquid oral formulations (LFs). Materials and Methods: Patients who had one or more seizures per month and prescribed with DDSF were recruited. Initially the patients were continued on DDSF for 4 months following which they were switched over to LF for the subsequent 4 months. Seizure frequencies and adverse drug effects (ADRs) were recorded every month for 8 months and plasma AED levels were estimated at the end of 4th and 8th months. Results: A total of 200 patients completed the study protocol. The median seizure frequencies per month with DDSF and LF were: partial seizures (20.5, 9.0; \( P < 0.001 \)), generalized tonic-clonic seizures (6.5, 2.0; \( P < 0.001 \)), myoclonic seizures (58.5, 29.0; \( P < 0.001 \)). Mean plasma drug levels ± SD (μg/ml) with DDSF and LF were: sodium valproate (48.2 ± 13.7, 69.1 ± 16.3; \( P < 0.001 \)), phenytoin sodium (5.0 ± 2.4, 12.8 ± 3.8; \( P < 0.001 \)), carbamazepine (4.5 ± 2.0, 11.5 ± 4.8; \( P < 0.001 \)) and phenobarbitone (14.1 ± 5.2, 25.4 ± 12.3, \( P < 0.001 \)). The incidence of treatment emergent ADRs was poor scholastic performance (25.5%), behavioral problems and dizziness/sedation (21.0%), somnolence/sleep disorders (19.5%). Conclusion: Patients treated with LF had better seizure control and optimal therapeutic drug levels and less adverse effects when compared to DDSF.

Keywords: Antiepileptic drugs, epilepsy, tablet splitting, therapeutic drug monitoring

Introduction

Epilepsy is one of the common neurological conditions in developing countries with about 10 million patients suffering from it in India.\(^1\) Many patients with epilepsy, especially from the lower socioeconomic strata do not receive optimal treatment as the drugs required for management of epilepsy are not available in the public health facilities.\(^2\) In India, clinicians prescribe split forms of the adult solid oral formulations for the management of pediatric epilepsy, since the liquid oral formulations (LFs) are not available in the public health-care setting. Caregivers of the patients split the tablets at home and give them to their wards.

The inaccuracy of splitting may significantly alter the dose administered; which may be clinically significant for drugs with a narrow therapeutic index, such as first-line antiepileptic drugs (AEDs), warfarin, levothyroxine, and digoxin.\(^3,5\) Some of the AEDs are manufactured in special oral formulations such as enteric coated, film-coated, extended release, and controlled-release formulations. These formulations should not be split or crushed before administration and if they are it could lead to undesirable effects.\(^6\)

The Better Medicines for Children resolution of the World Health Assembly Resolution WHA 60.20 states that child-friendly formulations and strengths must be provided for improving the use of medicines in children.\(^7\) LFs of AEDs are not readily available in the market in India.\(^8\) Even if they are available, they are extremely expensive. Hence, most public

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hospitals in India supply adult formulations to pediatric patients expecting the caregiver to split and administer the tablets. As we are aiming for universal health coverage in our country, the most efficacious, safe, and cost-effective treatment should be available at all public health facilities for children with epilepsy. However, cost considerations have prevented these being dispensed in the public health care facilities in India.

As split adult dosages of solid oral forms are routinely prescribed in children with epilepsy, we thought it prudent to compare the efficacy of the split adult solid oral formulation and the LFs in the management of epilepsy in children. This study investigates the efficacy and tolerability of LFs compared with divided doses of adult solid oral formulations (DDSF); and measures the plasma drug levels in pediatric epilepsy patients being treated with both these formulations.

**Materials and Methods**

**Study design**

This was a prospective, open-label, single arm, and crossover study, conducted in the outpatient pediatric epilepsy clinic of the Department of Pediatrics, JIPMER, Pondicherry during the period of January 2015 to April 2016. The analysis of AED levels was performed in the Department of Pharmacology, JIPMER, Puducherry, India. The study was approved by the Institutional Human Ethics Committee (JIP/IEC/2013/5/198) and JIPMER scientific advisory committee (JARC09/10/2013). This trial was registered in the Clinical Trial Registry of India (CTRI/2016/12/007602).

**Study participants**

After obtaining the written informed consent from the parent or legally accepted representative, children with epilepsy were recruited from the outpatient department of the pediatric epilepsy clinic. Children aged between one and seven years of either gender who were newly diagnosed as having epilepsy or receiving maintenance therapy with phenytoin sodium (PHY), carbamazepine (CBZ), sodium valproate (VPA) or phenobarbitone (PHT), either alone or in combination, who had one or more seizures (partial/tonic-clonic/absence seizures or combinations) per month treated with DDSF of AEDs were included in the study. Patients with special seizure syndromes or hepatic and renal failure were excluded from the study.

**Study drugs**

We chose four conventional first-line AEDs with narrow therapeutic indices that are routinely prescribed in our hospital: PHY, PHT, CBZ, and VPA. For adult solid oral formulations, the routinely prescribed generic formulation of PHY and VPA and the branded formulation (single brand) of CBZ and PHT were selected. For LFs, we provided one of the top brands available in the pharmacy store. Solid and LF characteristics are shown in Table 1. Each of the four different AED tablets and liquid formulations used in this study were of the same strength and from a single manufacturer with the same batch number.

**Study procedure**

Patients who satisfied the inclusion criteria and gave written informed consent were observed prospectively for 4 months and plasma drug concentrations were measured at the end of the 4th month. Then, the participants were switched over to LFs for the subsequent 4 months for observation and their plasma drug concentrations were once again measured at the end of the 8th month. During their monthly follow-up visit, seizure frequencies and adverse drug effects (ADRs) were recorded every month for 8 months by interviewing the caregivers.

**Estimation of plasma drug concentrations**

We collected 2.5 ml of venous blood just before the next dose, and estimated plasma drug levels at the end of 4 months using high-performance liquid chromatography (HPLC). To assess variation in plasma drug concentration, we developed and validated analytical methods for AEDs using HPLC (model no.: SIL-HTc Shimadzu HPLC system-10A VP).

| Table 1: Solid and liquid oral formulation characteristics of study drugs |
|---|
| Characteristic | Phenytoin | Valproate | CBZ | PHT |
| Adult solid oral formulations | | | | |
| Shape | Round | Round | Round | Round |
| Salt | Sodium | Sodium | - | - |
| Strength (mg) | 100 | 200 | 200 | 60 |
| Brand name | - | - | Carbine | Phenobarb |
| Type of tablet | Film coated | Enteric coated | Uncoated | Uncoated |
| Score-line | No | No | No | Yes |
| Tablet weight, mg (mean±SD) | 346.6±7.3 | 397.5±7.7 | 4.5±0.8 | 0.0±0.0 |
| Hardness, kg/cm² (mean±SD) | 9.0±1.0 | 3.5±0.4 | 4.5±0.8 | 0.0±0.0 |
| Friability (% weight loss) | 8.4 | 1.6 | |
| LF | | | | |
| Brand | Generic name | Encorate | Tegretal | Gardenal |
| Strength | 125 mg/5 ml | 200 mg/5 ml | 100 mg/5 ml | 20 mg/5 ml |
| Batch number | Sy-6116 | CEM0104 | 13Z046PH | GD54002 |
| Dosage form | Suspension | Solution | Suspension | Syrup |

SD=Standard deviation, CBZ=Carbamazepine, PHT=Phenobarbitone, LF=Liquid oral formulations
Phenytoin sodium, phenobarbitalone, and carbamazepine

After the blood sample was collected from children who received PHY, PHT, or CBZ, it was immediately centrifuged and plasma was separated. A mixture of chloroform: methanol (4:1) was prepared. A volume of 900 µl of spiked plasma standards (5, 10, 20, 40 µg/ml) and patient plasma samples were pipetted into 2 ml centrifuge tubes. Then, 20 µl of 1000 µg/ml internal standard (diazepam) was added. This was vortexed, and 600 µl was transferred to a clean conical flask. Four milliliter of the chloroform: methanol mixture was added to the above and the flask was sealed tightly with aluminum foil. This was shaken in an orbital shaker at 80 rpm at 25°C for 15 min. The solution was then transferred to a 15 ml centrifuge tube, centrifuged at 2500 rpm at 25°C for 5 min. The aqueous layer was discarded and the organic layer transferred to a clean glass tube (evaporation tube). The sample was evaporated using an evaporator at 60°C under nitrogen gas. The solution was reconstituted with 300 µl of Milli-Q water and vortexed for 2 min, then centrifuged briefly for 30 s using pulses not exceeding 1500 rpm. The above contents were transferred to a 0.5 ml microcentrifuge tube and centrifuged at 10,000 rpm for 5 min at 25°C. Finally, the supernatant was taken and transferred into HPLC vials, labeled and loaded in an autosampler rack. The runtime was 15 min, and the retention time for each AED was recorded. Buffer and solvent (30:70 v/v) run respectively. The detection was performed using an ultraviolet (UV) detector at 200 nm wavelength. The output of the UV detector was confirmed through photodiode array (PDA). The sample injection volume was 100 µl. The method was validated for specificity, precision, accuracy, sensitivity, linearity, and reproducibility as per ICH guidelines.[9,10] The sample injection volume was 100 µl. The method was validated for specificity, precision, accuracy, sensitivity, linearity, and reproducibility as per ICH guidelines.[11]

Sodium valproate

After blood was collected from children administered VPA, the samples were immediately centrifuged and plasma was separated. A volume of 1000 µl of spiked plasma standards (25, 50, 100, 200 µg/ml) was taken in 2.5 ml microcentrifuge tubes; plasma samples from patients and 1000 µl of acetonitrile was then added. Then, 10 µl of 100 µg/ml internal standard (diazepam) was added. The solution was vortexed for 1 min and centrifuged at 10,000 rpm for 10 min at 25°C. The entire supernatant layer was transferred to a clean glass evaporation tube. The solution was evaporated using an evaporator at 60°C under nitrogen gas. The solution was reconstituted with 300 µl of Milli-Q water and vortexed for 2 min, then centrifuged briefly for 30 s using pulses not exceeding 1500 rpm. The solution was then transferred to a 0.5 ml microcentrifuge tube and centrifuged at 10,000 rpm for 5 min at 25°C. Finally, the supernatant was transferred into HPLC vials, labeled, and loaded into an autosampler rack. Buffer and acetonitrile (40:60 v/v) run, respectively. The detection was performed using a UV detector at 210 nm wavelength. The output of the UV detector was confirmed with PDA. The sample injection volume was 100 µl, and the run time was 10 min.[12,13] The method was validated for specificity, precision, accuracy, sensitivity, linearity, and reproducibility as per ICH guidelines.

Statistical analysis

All the parameters were analyzed by using Excel 2010 (Microsoft Corporation, USA) and GraphPad InStat version 3.0 (GraphPad Software Inc., USA). Results are presented as mean ± standard deviation unless otherwise specified. Statistical comparison between seizure episodes after treatment with DDSF and LF was carried out using the Chi-square test. Comparison between mean plasma drug concentration levels before and after treatment with LF was carried out by the paired student’s t-test. P < 0.05 was considered statistically significant.

Results

A total of 450 patients were assessed for eligibility, of which 260 were recruited and 200 patients completed the entire study protocol. A flow diagram [Figure 1] shows the reasons for dropouts and exclusion. A total of 240 drugs were studied in 200 children. Patient demographic details are shown in Table 2. Complex partial seizures (36.5%) are the most commonly occurring seizure type in our pediatric population, followed by generalized tonic-clonic seizures (GTCS) (30.0%). 31.0% of

Table 2: Patient demographics and baseline characteristics

| Characteristics          | Value         |
|--------------------------|---------------|
| Total number of patients (n) | 200           |
| Age (months)             | 60.0±17.6     |
| Gender, n (%)            |               |
| Male                     | 110 (55.0)    |
| Female                   | 90 (45.0)     |
| Weight (kg)              | 15.8±5.1      |
| Height (cm)              | 98.2±21.3     |
| Body mass index (kg/m²)  | 16.9±3.7      |
| Time since diagnosis (months) | 36.0±19.2     |
| Duration of disease (months) | 23.5±15.2     |
| Etiology, n (%)          |               |
| Idiopathic               | 62 (31.0)     |
| Family history           | 53 (26.5)     |
| Hypoxic ischemic encephalopathy sequelae | 24 (12.0) |
| PT-AGA                   | 18 (9.0)      |
| Cerebral abscess         | 7 (3.5)       |
| Cerebral atrophy         | 6 (3.0)       |
| Microcephaly             | 6 (3.0)       |
| Spastic cerebral palsy   | 5 (2.5)       |
| Sepsis                    | 4 (2.0)       |
| Others                    | 15 (7.5)      |
| Seizure type, n (%)      |               |
| Generalized tonic-clonic seizures | 59 (30.0) |
| Complex partial seizures  |               |
| Right sided              | 31 (15.5)     |
| Left sided               | 43 (21.0)     |
| Simple partial seizures   | 15 (8.0)      |
| Myoclonic seizures       | 52 (26.0)     |

Values are expressed as mean±SD, unless otherwise specified. SD=Standard deviation, PT-AGA=Preterm-appropriate for gestational age.
seizures were idiopathic whereas 26.5% had a family history of epilepsy.

Majority of patients were recruited under monotherapy ($n = 150$, 75.0%) and 25% ($n = 50$) under combination therapy. VPA was the most prescribed drug in monotherapy ($n = 55$, 36.6%). Most prescribed two-drug combination was of VPA and CBZ, in 20 subjects (40.0%), followed by PHY and PHT combination used in 14 subjects (28.0%).

**Validation of the method**

Table 3 shows the intra- and inter-day precision and accuracy for the study drugs. All these parameters were within acceptable limits according to ICH guidelines. Figure 2 is a representative chromatogram of PHY, PHT, and CBZ; Figure 3 shows the same details for VPA. The retention times were: PHY 5.0 min, PHT 3.8 min, CBZ 5.5 min, and VPA 4.6 min.

As can be seen from Figure 4, the median seizure frequencies per month when children received with DDSF were nearly twice that of when LF were given. Mean plasma drug levels ($\mu g/ml$) and percentage of patients outside the therapeutic range after treatment with DDSF and LF are shown in Table 4.

Treatment emergent adverse drug events (TEAE) are shown in Table 5. There was no withdrawal of patients due to a TEAE. The overall incidence of TEAEs was higher with DDSF (60.0%) compared to LF (40.0%). The most frequently reported TEAEs ($\geq 15\%$ patients in either group) were poor scholastic performance (25.5%) followed by behavioral problems, dizziness/sedation (21.0%) and others.

**DISCUSSION**

Treatment with LFs showed better seizure control compared to DDSF. More than 50% of seizure reduction was seen in GTCS (71.4%), partial seizures (57.0%) and myoclonic

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**Figure 1:** Flowchart of patient recruitment

**Figure 2:** Representative chromatogram of phenytoin sodium, phenobarbitone, carbamazepine
seizures (50.9%). All the AED treatment with liquid formulations maintained optimum therapeutic drug concentration unlike treatment with DDSF. Greater than 85% of patients’ plasma drug concentration of each drug was within the optimal therapeutic window (PHY 91.7%, PHT 88.6%, CBZ 86.7%, VPA 85.2%) with LF. No previous studies are available to compare or correlate our findings. To the best of our knowledge, this is the first study comparing the efficacy and safety of treatment with DDSF and LF.

Our earlier study shows that 68%–78% of patients had suboptimal plasma drug concentrations outside the therapeutic range when treated with DDSF. Although there are no comparable studies of AEDs, studies with other groups of drugs found no difference in the lipid profiles of patients treated with split or whole statin tablets. The findings of these studies are contradictory to our findings; this may be because the endpoint was change in lipid levels rather than plasma drug concentration as well as the fact that the formulation may be suited for splitting. In addition, as the...
studies were in adults patients received one or more whole tablets along with split forms. Furthermore, monitoring of AED levels is known to guide therapy, as therapeutic drug monitoring is routine in the management of epilepsy. Therefore, drug levels outside the normal therapeutic range in epilepsy is a cause for concern.

In our study, 75%–80% of AED prescriptions were prescribed as split tablets. This percentage is far higher than in other studies because our study involved children aged one to 7 years whereas other studies have involved a mixed group of patients. Despite it being well-known that coated, unscored, and special formulations such as sustained-release and controlled-release, should not be split, patients are prescribed such formulations and advised to split them as they are the only formulations available for prescribing in our hospital. VPA was the most commonly prescribed drug as well as in split forms followed by PHY. A study conducted in the North India by Suman and Gosavi reported similar finding. Interestingly, both of these tablets were special dosage forms (enteric and film-coated).

Table splitting exposes the core of the tablet to the external environment; the split tablets may not have the same stability profile as determined by the manufacturer. Tablets split and returned to a storage bottle may become more friable and fragment easily. In addition, dissolution may change (because of change in surface area), and degradation may be enhanced (because of change in exposure to air, moisture, or light). VPA, which is hygroscopic in nature, was split and stored for 24 or 48 h, it absorbed water and melted before being given to the children. In this situation, drug content reduced by more than 10%.

Poor scholastic performance is one of the foremost adverse effects reported by the caregivers in children aged more than 5 years in our study. A study in the North India by Bansal et al., reported similar results. This poor scholastic performance is due to psychiatric and behavioral problems associated with epilepsy and AEDs. Behavioral problems are the second most commonly reported adverse report in our study as has been concurred by Nadkarni and Devinsky. Elevated liver enzymes mainly alanine aminotransferase was reported more than 5.0% in our study. Hepatotoxic effects of AEDs are well established. VPA, phenytoin, and CBZ predominantly undergoes hepatic metabolism by enzyme induction. Production of toxic metabolites, pharmacokinetic changes, treatment with longer duration and underlying liver disease are considered as major causes of AED-induced hepatotoxicity. Various studies have revealed the link between AEDs and hepatotoxicity. In the present study, 16 participants from VPA and 11 from CBZ developed weight gain. Drug-induced weight gain is an adverse effect of VPA and CBZ leading to noncompliance with therapy and to the aggravation of comorbid conditions related to obesity.

To the best of our knowledge, this is the first study to compare the divided doses of solid oral formulations with liquid formulations in children. We selected the best study design (crossover) to test the hypothesis where control group is not needed, and confounders such as pharmacogenomics, duration of the treatment and patient population may not affect plasma drug levels. We prospectively conducted the study over a period of 8 months with seizure frequency and plasma drug levels as primary endpoints. The major limitation of this study was that we studied only first-line AEDs. Second-generation

### Table 3: Inter-day and intra-day precision and accuracy for the determination of phenytoin sodium, phenobarbitone, carbamazepine, and sodium valproate in human plasma

| Nominal concentration (µg/mL) | Percentage of RSD | Accuracy (%) |
|------------------------------|-------------------|--------------|
|                              | Intra-daya | Inter-dayb | Intra-dayc | Inter-dayc |
| PHY                          |           |           |           |           |
| 5                            | 1.62      | 2.00      | 98.12     | 97.67     |
| 10                           | 1.43      | 1.95      | 98.01     | 97.15     |
| 20                           | 1.11      | 1.86      | 98.87     | 97.19     |
| 40                           | 0.89      | 1.80      | 98.90     | 98.00     |
| PHT                          |           |           |           |           |
| 5                            | 1.79      | 1.89      | 98.25     | 98.00     |
| 10                           | 1.61      | 1.80      | 99.01     | 98.16     |
| 20                           | 1.64      | 1.73      | 98.78     | 98.19     |
| 40                           | 1.12      | 1.52      | 99.12     | 99.02     |
| CBZ                          |           |           |           |           |
| 5                            | 1.11      | 1.89      | 99.22     | 98.56     |
| 10                           | 1.01      | 1.67      | 99.34     | 99.01     |
| 20                           | 0.68      | 1.43      | 99.19     | 99.00     |
| 40                           | 0.67      | 1.21      | 99.67     | 99.14     |
| VPA                          |           |           |           |           |
| 25                           | 2.56      | 3.01      | 97.27     | 96.28     |
| 50                           | 2.45      | 2.67      | 97.78     | 96.18     |
| 100                          | 2.21      | 2.89      | 97.12     | 96.01     |
| 200                          | 2.12      | 2.65      | 97.56     | 96.29     |

*aMean of six replicates, bMean of 3 days, RSD=Relative standard deviation, PHY=Phenytoin sodium, CBZ=Carbamazepine, VPA=Sodium valproate, PHT=Phenobarbitone*

### Table 4: Mean plasma drug concentrations of antiepileptic drugs after treatment with divided doses of adult solid oral formulations and liquid oral formulations

| Drug | Plasma drug levels (µg/mL) with DDSF | Plasma drug levels (µg/mL) with LF | P   |
|------|--------------------------------------|-----------------------------------|-----|
| PHY  | 5.0±2.4 (84.6)                       | 12.8±3.8 (83.3)                   | <0.001 |
| CBZ  | 4.5±2.0 (80.0)                       | 11.5±4.8 (13.3)                   | <0.001 |
| VPA  | 48.2±13.7 (87.5)                     | 69.1±16.3 (19.4)                  | <0.001 |
| PHT  | 14.1±5.2 (76.9)                      | 25.4±12.3 (11.4)                  | <0.001 |

All values are expressed as (mean±SD). The figures within parentheses denote the percentage of samples outside the therapeutic range. Normal therapeutic range (µg/mL) - PHY=10–20, VPA=50–100, CBZ=6–12, PHT=15–35. DDSF=Divided doses of adult solid oral formulations, LF=Liquid oral formulations, PHY=Phenytoin sodium, CBZ=Carbamazepine, VPA=Sodium valproate, PHT=Phenobarbitone, SD=Standard deviation
AEDs were not included as they are not commonly prescribed in our setting. Dissolution parameters after splitting were not studied which may have contributed to substantiate the findings.

**Conclusion**

Pediatric patients treated with LFs had better seizure control compared to those given DDSF. Patients treated with liquid formulations maintained optimum therapeutic drug concentration compared to DDSF and more than eighty percentage of patients’ plasma drug concentrations were within the optimal therapeutic window. Liquid formulations are well tolerated and lesser ADRs were reported. Patients, as well as caregivers, had showed good adherence toward the treatment. Liquid formulations are preferred over divided doses of solid oral formulations for better control of seizures and lesser adverse effects as well as better adherence to treatment. We recommend that children with epilepsy should be treated with liquid formulations of AEDs which will lead to better seizure control, optimal therapeutic drug levels and safety profile.

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**Conflicts of interest**

There are no conflicts of interest.

**Table 5: Summary of treatment emergent adverse events with both formulations**

| Adverse drug reaction                  | VPA (n) | PHY (n) | CBZ (n) | PHT (n) | Total (%) |
|----------------------------------------|---------|---------|---------|---------|-----------|
|                                        | DDSF    | LF      | DDSF    | LF      | DDSF     | LF      | DDSF    | LF      | DDSF    | LF      |          |
| Poor scholastic performance            | 13      | 9       | 8       | 5       | 7        | 5       | 2       | 2       | 51       | 100      |
| Behavioral problems                    | 12      | 8       | 6       | 4       | 7        | 5       | 0       | 0       | 42       | 100      |
| Dizziness/sedation                     | 8       | 6       | 7       | 4       | 7        | 5       | 3       | 2       | 42       | 100      |
| Somnolence                             | 7       | 5       | 6       | 4       | 8        | 6       | 2       | 1       | 39       | 100      |
| Nausea                                 | 7       | 5       | 5       | 4       | 5        | 3       | 3       | 2       | 34       | 100      |
| Weight gain                            | 10      | 6       | 0       | 0       | 7        | 4       | 0       | 0       | 27       | 100      |
| Fatigue                                | 5       | 3       | 2       | 2       | 5        | 3       | 2       | 2       | 24       | 100      |
| Headache                               | 7       | 4       | 2       | 2       | 3        | 2       | 1       | 1       | 22       | 100      |
| Rash                                   | 2       | 1       | 0       | 0       | 9        | 6       | 2       | 2       | 22       | 100      |
| Increased appetite                      | 7       | 5       | 0       | 0       | 5        | 4       | 0       | 0       | 21       | 100      |
| Vomiting                               | 4       | 2       | 4       | 3       | 4        | 2       | 1       | 1       | 21       | 100      |
| Abdominal pain                         | 7       | 4       | 2       | 2       | 3        | 2       | 1       | 0       | 21       | 100      |
| Elevated ALT                           | 8       | 5       | 1       | 1       | 0        | 0       | 0       | 0       | 15       | 75.0     |
| Decreased appetite                     | 0       | 0       | 4       | 3       | 0        | 0       | 0       | 0       | 7        | 37.5     |
| Depression                             | 2       | 2       | 1       | 0       | 1        | 1       | 0       | 0       | 7        | 37.5     |
| Gum hypertrophy                        | 0       | 0       | 3       | 2       | 0        | 0       | 1       | 0       | 6        | 30.0     |
| Hair loss                              | 1       | 1       | 0       | 0       | 1        | 1       | 0       | 0       | 4        | 20.0     |

VPA=Sodium valproate, PHY=Phenytoin sodium, CBZ=Carbamazepine, PHT=Phenobarbapine, ALT=Alanine aminotransferase, DDSF=Divided doses of adult solid oral formulations, LF=Liquid oral formulations

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