Pharmacovigilance in Pediatric Patients with Epilepsy Using Antiepileptic Drugs

Dorota Kopciuch 1,*, Krzysztof Kus 1, Jędrzej Fliciński 2, Barbara Steinborn 2, Anna Winczewska-Wiktor 2, Anna Paczkowska 1, Tomasz Zaprutko 1, Piotr Ratajczak 1 and Elżbieta Nowakowska 3

1 Department of Pharmacoeconomics and Social Pharmacy, Karol Marcinkowski University of Medical Sciences, Rokietnicka 7, 60-806 Poznan, Poland; kkus@ump.edu.pl (K.K.); aniapazkowska@ump.edu.pl (A.P.); tomekzaprutko@ump.edu.pl (T.Z.); p_ratajczak@ump.edu.pl (P.R.)
2 Department of Developmental Neurology, Karol Marcinkowski University of Medical Sciences, Przybyszewskiego 49, 60-355 Poznan, Poland; flicinski@hotmail.com (J.F.); bstein@ump.edu.pl (B.S.); awwiktor@ump.edu.pl (A.W.-W.).
3 Department of Pharmacology and Toxicology, Institute of Health Sciences, Collegium Medicum, University of Zielona Góra, Licealna 9 Street, 65-417 Zielona Góra, Poland; elapharm@ump.edu.pl (E.N.)

* Correspondence: dorota.koli@vp.pl; Tel./Fax: +48-618-546-894

Abstract: Objective: To investigate the occurrence of adverse effects of antiepileptic drugs (AEDs) in pediatric epileptic patients on mono- or polytherapy. Method: We evaluated eighty consecutive patients that met the following inclusion criteria: aged ≤18 years; diagnosed with epilepsy for at least one year; a stable dose of AED for at least three months; verbal consent to participation in the study. Patients were asked if they had experienced any adverse drug reaction (ADR) related to the AED. Afterward, regardless of the answer, they were interviewed based on a detailed semi-structured questionnaire about the presence of ADRs associated with the AED. The data were analyzed regarding the use of monotherapy or polytherapy. Results: Ninety-seven percent of the patients reported having experienced ADRs related to AEDs. The greatest number of seizures affected the group of patients treated with monotherapy (both at baseline and at followup), but the greatest number of ADRs were observed among patients treated with polytherapy. In patients on monotherapy, the most frequent ADRs reported at baseline included fatigue and somnolence, and among patients with polytherapy, it was fatigue and hair loss. Conclusion: Children on polytherapy were significantly more likely to develop ADRs compared to those on monotherapy, but a statistically significant improvement in seizure frequency was also observed in the group of patients on polytherapy. Pharmacovigilance is very important in children with AEDs, so that ADRs can be identified early and managed appropriately.

Keywords: antiepileptic drugs; pharmacovigilance; epilepsy; adverse drug reactions; adverse events; pediatric population; children

1. Introduction

Epilepsy is a chronic disorder characterized by episodic gratuitous seizures. Many individuals with epilepsy have a combination of various types of seizures and may have other signs of neurological complications as well [1]. Most patients with epilepsy rely on medical treatment with antiepileptic drugs (AEDs) to achieve control of their seizures [2].

The overall aim in the treatment of epilepsy should be complete control of seizures and no adverse reaction due to medication. In particular, treatment of pediatric epilepsy requires a careful evaluation of the safety and tolerability profile of AEDs to avoid or minimize adverse events (AEs) on various organs, hematological parameters, growth, and pubertal, motor, cognitive, and behavioral development as much as possible [3–7].

Polytherapy is sometimes used in refractory epilepsy despite a significant increase in the number of the side effects [8,9].
Adverse effects of AEDs are typical and can have a significant effect on the quality of life of the patients and add up to treatment letdown in about 40% of admitted patients. The adverse effect summaries of AEDs vary prominently and are often a decisive aspect of drug choice because of the similar efficacy proportions presented by most AEDs. The most communal adverse drug reactions (ADRs) are dose-related and reversible [10].

The aim of this study was to investigate the occurrence of ADRs of AEDs in pediatric epileptic patients on mono- or polytherapy.

2. Method

The study was conducted at the department of developmental neurology in Poland, between 2019 and 2020. We evaluated consecutive patients that met the following inclusion criteria: aged ≤18 years, diagnosis of epilepsy for at least one year, a stable dose of AED for at least three months, and verbal consent to participation in the study.

Patients (or/and their caregivers) were asked if they had any ADRs related to the AEDs. After that, regardless of the answer, they were interviewed based on a detailed questionnaire about the presence of ADRs associated with the AEDs (Supplementary Materials). We also assessed specifically the ADRs in the last 3 months.

Patients were interviewed twice during the study, at baseline and followup period.

“Baseline” describes the average number of ADRs per month at the beginning of the study. “Followup” means the average number of ADRs per month over the last 3 months after beginning of the study.

In order to assess whether and how AEDs impact the incidence of ADRs in pediatric patients with epilepsy, the patients’ case histories were analyzed in terms of pharmacotherapy used. Then, the patients were divided into groups as per their treatment, monotherapy or polytherapy. The average number of seizures was calculated for each group. Comparisons of efficacy for treatment regimens (monotherapy vs. polytherapy) were calculated as within-patient ratios of the average seizure frequency at followup, divided by the average seizure frequency at baseline in each group.

To make our results comparable with the metric usually reported in AED clinical trials, we reported the percentage reduction in normalized seizure frequency as (1-SFR) × 100 [11].

3. Statistical Analysis

The seizure frequency ratio (SFR) data were obtained after log-transformation of the data and are expressed as means (average) ± standard deviation (SD) and median with 95% confidence intervals (CIs). We used log-transformation of SFR statistics in order to provide a metric symmetrical around SFR = 1 (representing no change); that is, so that small SFRs, reflecting a highly effective trial, would be equally weighted against highly ineffective trials where SFR was high [11].

The data distribution pattern was not normal (unlike a Gaussian function). Statistical analyses for SFR were carried out using the nonparametric Wilcoxon test for paired data. Significant differences between % of group results were determined by analysis of the Test for Proportions.

The study was approved by the Bioethics Committee of the Poznań University of Medical Sciences.

4. Results

Eighty epileptic children subjects were included in the study. In total, 53.75% experienced generalized epileptic seizures and 20.00% focal epileptic seizures (Table 1). The age ranged from 2 to ≤18 years. The average duration of epilepsy in study group subjects was 4.11 ± 1.22 years. The children were taking on average 1.79 ± 0.80 AEDs (Table 1).
Table 1. Demographic and clinical data (at baseline).

| Demographic and clinical data | Value |
|-------------------------------|-------|
| Age; average ± SD             | 8.33 ± 4.37 |
| Gender; n (M/F)               | 38/42 |
| Duration of epilepsy, years (average ± SD) | 4.11 ± 1.22 |

| Type of seizures; n (%)       |       |
|-------------------------------|-------|
| Generalized                  | 43 (53.75%) |
| Focal                         | 16 (20.00%) |
| Other                         | 21 (26.25%) |

| Therapeutic scheme            |       |
|-------------------------------|-------|
| Monotherapy; n (%):           | 34 (42.50) |
| Valproate (%)                 | 39.21% |
| Phenytion (%)                 | 23.31% |
| Carbamazepine (%)             | 19.80% |
| Clobazam (%)                  | 10.12% |
| Levetracetam (%)              | 30.32% |
| Vigabratrin (%)               | 17.68% |
| Oxcarbazepine (%)             | 13.27% |
| Topiramate (%)                | 11.40% |
| Lacosamide (%)                | 2.63% |
| Lamotrigine (%)               | 18.88% |
| Polytherapy; n (%)            | 46 (56.50) |
| 2 drugs (%)                   | 61.94 |
| 3 drugs (%)                   | 38.06 |
| Average AEDs (average ± SD):  |       |
| Monotherapy                   | 32.22 ± 12.21 |
| Polytherapy                   | 21.12 ± 7.31 |

SD—standard deviation; AED—antiepileptic drugs.

The largest percentage of children with epilepsy were on levitracetam (LEV) (30.32%) followed by lamotrigine (LTG) (18.88%) and vigabatrin (VGB) (17.68%). The most frequent second generation of AEDs were valproate (VPA) (39.21%) and phenytoin (PHT) (23.32%) (Table 1). Ninety-seven percent of the patients reported having experienced an ADR related to AEDs (p < 0.001). In patients on monotherapy, the most frequent ADRs reported at baseline included fatigue (47.09%), and somnolence (55.88%) (Table 2); and at followup, it was emotional liability (50.00%), fatigue (55.88%), psychomotor agitation (61.76%), anxiety (47.05%), and somnolence (58.82%) (Table 2).
In patients on polytherapy, the most frequent ADRs reported at baseline included fatigue (41.30%) and hair loss (34.78%) (Table 2), and at followup, they reported fatigue (58.69%), psychomotor agitation (50.00%), anxiety (50.00%), emotional liability (47.82%), and memory impairment (52.17%) (Table 2).

Statistically significant differences in the incidence of individual ADRs occurred between baseline and followup both in patients on monotherapy and those on polytherapy (Table 2). In both groups, incidence of such ADRs as emotional liability, psychomotor agitation, aggressiveness, and anxiety increased during the followup period. Moreover, in the monotherapy group, tremor and weight gain were much more frequently reported during the followup than during the baseline period. Patients on polytherapy, on the other hand, reported headache, dyspepsia, memory impairment, and lack of focus much more frequently in the followup period than during the baseline period (Table 2).

A statistically significant difference in incidence of hair loss \((p = 0.0187)\) and diplopia or blurred vision \((p = 0.0505)\) was observed at baseline in the group of patients on polytherapy compared to those on monotherapy. Conversely, in the followup period, statistically significant differences were found for dyspepsia \((p = 0.0531)\) and lack of focus \((p = 0.0003)\) in the group of patients on polytherapy compared to those on monotherapy (Table 2).

In the followup period, statistically significant differences in clinical data between patients on monotherapy and polytherapy were observed in virtually each of the study clinical parameters, i.e., in the average number of ADRs per month \((p < 0.0001)\), average seizure frequency per month \((p < 0.0001)\), average number of hospitalization days per month \((p = 0.0005)\), and average number of outpatient neurologist visits per month \((p = 0.0002)\) (Table 3).

### Table 2. Frequency of adverse events in the last three months versus since the beginning of the study according with treatment groups.

| Adverse Drug Reactions                  | Monotherapy \((n = 34)\) | Polytherapy \((n = 46)\) | \(p\) Value Baseline vs. Followup | \(p\) Value Baseline vs. Polytherapy | \(p\) Value Baseline vs. Followup |
|----------------------------------------|--------------------------|---------------------------|-----------------------------------|-------------------------------------|-----------------------------------|
| Emotional liability                    | 3 (8.82)                 | 17 (50.00)                | 0.0002                            | <0.0001                             | 0.9950                            |
| Fatigue                                | 16 (47.09)               | 19 (55.88)                | 0.4684                            | 0.0953                             | 0.6058                            |
| Psychomotor agitation                  | 3 (8.82)                 | 21 (61.76)                | <0.0001                           | 0.9838                             | 0.2959                            |
| Aggressiveness                         | 4 (11.76)                | 14 (41.17)                | 0.0060                            | 0.6058                             | 0.8016                            |
| Anxiety                                | 2 (5.94)                 | 16 (47.05)                | 0.0002                            | 0.9950                             | 0.8471                            |
| Headache                               | 5 (14.70)                | 10 (29.41)                | 0.1435                            | 0.2279                             | 0.3676                            |
| Hair loss                              | 4 (11.76)                | 6 (17.64)                 | 0.4936                            | 0.1008                             | 0.8278                            |
| Skin reactions                         | -                        | 6 (17.64)                 | No Data                           | 1.0000                             | No Data                           |
| Diplopia or blurred vision             | 3 (8.82)                 | 6 (17.64)                 | 0.2831                            | 0.0505                             | 0.1327                            |
| Dyspepsia                              | -                        | 9 (26.51)                 | No Data                           | No Data                            | 0.0531                            |
| Gingival hypertrophy                   | 10 (29.41)               | 5 (14.70)                 | 0.1435                            | No Data                            | No Data                           |
| Tremor                                 | 3 (8.82)                 | 11 (32.35)                | 0.0164                            | No Data                            | No Data                           |
| Weight gain                            | 2 (5.92)                 | 8 (23.52)                 | 0.0405                            | No Data                            | No Data                           |
| Dizziness                              | 4 (11.76)                | 9 (26.51)                 | 0.1221                            | No Data                            | No Data                           |
| Somnolence                             | 19 (55.88)               | 20 (58.82)                | 0.8064                            | No Data                            | No Data                           |
| Memory impairment                      | 7 (20.58)                | 12 (35.10)                | 0.1820                            | No Data                            | No Data                           |
| Sleep disturbance                      | 6 (17.64)                | 8 (23.52)                 | 0.5487                            | No Data                            | No Data                           |
| Lack of concentration                  | 1 (2.94)                 | 4 (11.76)                 | 0.1634                            | No Data                            | No Data                           |
Table 3. Clinical and statistical data of pediatric patients with epilepsy.

|                                | Baseline (n = 34) | Followup (n = 46) |
|--------------------------------|-------------------|-------------------|
| **Average number of ADRs per month (±SD)** | 5.02 ± 0.62       | 6.40 ± 1.65       |
|                                | p = 0.7536        | p < 0.0001        |
| **Average seizure frequency per month (±SD)** | 32.22 ± 12.21     | 27.47 ± 12.45     |
|                                | p < 0.0001        | p < 0.0001        |
| **Average number of hospitalization days per month** | 3.19 ± 0.80       | 2.79 ± 1.02       |
|                                | p < 0.0001        | p < 0.0001        |
| **Average number of outpatient neurologist visits per month** | 2.01 ± 0.29       | 1.21 ± 0.78**     |
|                                | p < 0.0001        | p = 0.0002        |

SD—standard deviation; AE—adverse events; * statistically significant difference (p < 0.0001) vs. baseline in polytherapy; # statistically significant difference (p = 0.0002) vs. baseline in polytherapy; ** statistically significant difference (p < 0.0001) vs. baseline in monotherapy.

In the baseline period, statistically significant differences in clinical data between patients on monotherapy and polytherapy were not observed only in terms of the average number of AEs per month (p = 0.7536) (Table 3).

Similar observations were made in the analysis of occurrence of statistically significant differences in clinical data between the measurements made at baseline and at followup in each of the groups (Table 2). The noted differences were not observed only in terms of the average number of AEs per month in patients on monotherapy (Table 2).

The analysis of average seizure frequency rates (SFRs) depending on the pharmacotherapy regimen (mono- vs. polytherapy) has shown that, both at baseline and at followup, the greatest number of seizures affected the group of patients treated with monotherapy (32.22 ± 12.21 at baseline; 27.47 ± 12.45 at followup) (Table 4). The average SF in patients treated with polytherapy was estimated at 21.12 ± 7.31 at baseline and 15.98 ± 5.19 at followup (Table 4).

Table 4. Comparative analysis of the pharmacotherapy regimen efficacy among pediatric patients with epilepsy.

| Treatment Groups | Average SF ± SD [Med./95% CIs] in Baseline (n = 34) | Average SF ± SD [Med./95% CIs] in Followup (n = 46) | Average SFR ± SD [95% CIs] | Average % Decrease (Increase) in Seizure Frequency in Followup vs. Baseline |
|------------------|-------------------------------------------------------|------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------|
| Monotherapy      | 32.22 ± 12.21 [15.14, 40.85]                          | 27.47 ± 12.45 [11.48, 18.53]                         | 0.85                       | 15                                                                              |
| Polytherapy      | 21.12 ± 7.31 [24.84, 48.24]                           | 15.98 ± 5.19 [14.14, 21.96]                          | 0.76                       | 24                                                                              |

SF—seizure frequency; SFR—seizure frequency ratio; NS—no significance; SD—standard deviation; AEDs—antiepileptic drugs; CIs-confidence intervals.

A statistically significant improvement in seizure frequency was observed in the group of patients on polytherapy (Table 4). In the group of patients on monotherapy, average seizure frequency was reduced by 15% compared to seizure frequency at the baseline, while in the group on polytherapy, seizure frequency reduction compared to the baseline amounted to 24% (Table 4).

5. Discussion

About one-third of patients receiving AEDs in this study developed at least one ADR during the treatment. Similar AED prevalence pattern has been reported in other studies [12–15].

The number of patients on polytherapy in our study was higher than what was reported in previous studies in the UK [14] and in India [16]. This may result from the fact that many cases of epilepsy in our society are associated with other neurologic disorders,
and this may contribute to the difficulty in controlling the seizures with a single AED. Monotherapy is viewed as the initial and preferred option for treating epilepsy, the choice of the drug depends on seizure type and the drug’s efficacy balanced against possible side-effects [17].

In a study conducted in the UK [14], most of the children received monotherapy, with only 25% receiving polytherapy. Various studies suggest that AED used as monotherapy is effective in 60–70% of children [18,19]. Additional drugs in refractory patients have been shown to be only marginally beneficial [20]. Polytherapy entails a greater risk of drug toxicity in pediatric patients in general [21], especially those receiving AEDs [22]. More children receiving polytherapy in this study developed ADRs, with up to a three-fold higher incidence of ADRs compared to monotherapy. This is consistent with earlier reports [14,16,22].

Unfortunately, most new AEDs are tested by the pharmaceutical companies as an add-on therapy, and drug toxicity is poorly described. This encourages clinicians to use polytherapy in epilepsy.

A U.S. study of 314 adults found that 44% of the patients were on monotherapy with the remaining 56% of patients on polytherapy [23]. Similar proportions were found in a European study assessing the quality of life of over 5000 patients: 47% of patients were reported to be receiving monotherapy, and 36% were taking 2 AEDs (12% were on 3, 1% on 4 or more, and 4% were not receiving any medication). The drugs most commonly taken were carbamazepine (53%), sodium valproate (33%), and phenytoin (25%) [24].

Although ADRs were more frequent in patients on polytherapy, improvement of clinical parameters such as lower seizure frequency, fewer outpatient neurologist visits, or fewer hospitalization days was observed in this group. The question remains, however, whether the polytherapy may be responsible for this reduction in, for example, seizure control; it is also possible that the second drug alone might be effective. Side effects increase with polytherapy; it is unclear, however, whether this is caused by the number of medications or the total drug load.

The main ADRs identified in this study were behavioral problems such as emotional liability, anxiety, fatigue, and psychomotor agitation, which were comparable to those from another study [25].

In our study the number of adverse effects was similar in both the mono- and polytherapy group. Individual analysis of each side effect, diplopia, anxiety, dyspepsia, dizziness, memory impairment, sleep disturbance, and lack of focus, showed that they were found to occur more frequently in patients on polytherapy. Similarly to our study results, several other studies have shown that the incidence of adverse effects increases with the number of drugs [26].

Many studies show that comorbidity in epilepsy is a major issue currently, and depression and related symptoms, such as fatigue and lack of focus, are some of the main conditions associated with epilepsy [27–29].

Furthermore, the adverse effects of AEDs and emotional/behavioral problems may have the strongest negative influence on the patient’s perception of their current health. The adverse impact of emotional problems on the quality of life of epileptic patients requires an investigation of their presence in every pediatric patient with epilepsy [30].

6. Limitation

We are aware that our study had several limitations. Firstly, our study was an observational study and not a randomized controlled trial; therefore, selection bias could have affected the results. The insufficient number of patients recruited may be another limitation. Much larger studies are required to adequately determine the ADRs of AEDs in mono- or polytherapy.
7. Conclusions

To conclude, children on polytherapy were significantly more likely to develop ADRs compared to those on monotherapy. Physicians should give AED polytherapy only when the maximum therapeutic doses of monotherapy are ineffective. Pharmacovigilance is very important in children on AEDs, so that ADR can be identified early and managed appropriately. Both clinicians and parents should monitor AED-treated children for adverse reactions, especially for behavioral problems such as emotional liability and anxiety, and fatigue, somnolence, and psychomotor agitation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph19084509/s1, Supplementary File: Questionnaire.

Author Contributions: D.K.—contributions to the conception, design of the work, analysis, interpretation of data, revision and approving the submitted version. J.F., B.S., A.W.-W. and A.P.—contributions to the analysis, revision and approving the submitted version. T.Z., P.R., E.N. and K.K.—contributions to the interpretation of data; revision and approving the submitted version. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: We confirm that we have read the journal’s position on issues involved in ethical publication, and we confirm that this report is consistent with those guidelines. The study was approved by the Bioethics Committee at Poznan University of Medical Sciences. Verbal informed consent was obtained from all individual pharmacists included in the study.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hilgers, A.; Schaefer, M. Systematic Adverse Drug Reaction Monitoring of Patients Under Newer Antiepileptic Drugs Using Routine Clinical Data of Inpatients. Drugs Real World Outcomes 2016, 3, 209–221. [CrossRef]
2. Gosavi, D.; Suman, A. Study of Adverse Drug Effects of Antiepileptic Drugs Used in Pediatric Patients in a Tertiary Care Rural Hospital—A Pharmacovigilance Study. J. Young Pharm. 2017, 9, 60–64. [CrossRef]
3. Moavero, R.; Pisani, L.R.; Pisani, F.; Curatolo, P. Safety and Tolerability Profile of New Antiepileptic Drug Treatment in Children with Epilepsy. Expert Opin. Drug Saf. 2018, 17, 1015–1028. [CrossRef]
4. Bazil, C.W. Sleep and Epilepsy. Semin. Neurol. 2002, 22, 321–327. [CrossRef]
5. Aeby, A.; Ceulemans, B.; Lagae, L. Treatment of Focal-Onset Seizures in Children: Should This Be More Etiology-Driven? Front Neurol. 2022, 13, 84276. [CrossRef]
6. Holland, K.D. Efficacy, Pharmacology, and Adverse Effects of Antiepileptic Drugs. Neurol. Clin. 2001, 19, 313–345. [CrossRef]
7. Jallon, P.; Picard, F. Bodyweight Gain and Anticonvulsants: A Comparative Review. Drug Saf. 2001, 24, 969–978. [CrossRef] [PubMed]
8. Deckers, C.L.P. Place of Polytherapy in the Early Treatment of Epilepsy. CNS Drugs 2002, 16, 155–163. [CrossRef]
9. Salas-Puig, J. Rational anti-epileptic polytherapy. Drug interactions and choice of treatment. Rev. Neurol. 2000, 30, 886–889. [PubMed]
10. Perucca, E. An Introduction to Antiepileptic Drugs. Epilepsia 2005, 46 (Suppl. S4), 31–37. [CrossRef]
11. Poolos, N.P.; Castagna, C.E.; Williams, S.; Miller, A.B.; Story, T.J. Association between Antiepileptic Drug Dose and Long-Term Response in Patients with Refractory Epilepsy. Epilepsy Behav. 2017, 69, 59–68. [CrossRef] [PubMed]
12. Hamer, H.M.; Dodel, R.; Strzelczyk, A.; Balzer-Geldsetzer, M.; Resse, J.P.; Schofski, O.; Graf, W.; Schwab, S.; Knake, S.; Oertel, W.H.; et al. Prevalence, Utilization, and Costs of Antiepileptic Drugs for Epilepsy in Germany—A Nationwide Population-Based Study in Children and Adults. J. Neurol. 2012, 259, 2376–2384. [CrossRef] [PubMed]
13. Ackers, R.; Murray, M.L.; Besag, F.M.C.; Wong, I.K.C. Prioritizing Children’s Medicines for Research: A Pharmaco-Epidemiological Study of Antiepileptic Drugs. Br. J. Clin. Pharmacol. 2007, 63, 689–697. [CrossRef]
14. Anderson, M.; Egunsola, O.; Cherrill, J.; Millward, C.; Fakis, A.; Choonara, I. A Prospective Study of Adverse Drug Reactions to Antiepileptic Drugs in Children. BMJ Open 2015, 5, e008298. [CrossRef] [PubMed]
15. Kwong, K.L.; Tsui, K.W.; Wu, S.P.; Yung, A.; Yau, E.; Eva, F.; Ma, C.K.; Cherk, S.; Liu, K.T.; Cheng, W.W.; et al. Utilization of Antiepileptic Drugs in Hong Kong Children. Pediatr. Neurol. 2012, 46, 281–286. [CrossRef] [PubMed]
16. Suke, S.G.; Kosta, P.; Negi, H. Role of Pharmacovigilance in India: An overview. Online J. Public Health Inform. 2015, 7, e223. [CrossRef]
17. Browne, T.R.; Holmes, G.L. Handbook of Epilepsy; Jones & Bartlett Learning: Burlington, MA, USA, 2008; ISBN 978-0-7817-7397-3.
18. Dudley, R.W.R.; Penney, S.J.; Buckley, D.J. First-Drug Treatment Failures in Children Newly Diagnosed with Epilepsy. Pediatr. Neurol. 2009, 40, 71–77. [CrossRef]
19. Ma, M.-S.; Ding, Y.-X.; Ying, W.; Fang, F.; Ding, C.-H.; Zou, L.-P. Effectiveness of the First Antiepileptic Drug in the Treatment of Pediatric Epilepsy. Pediatr. Neurol. 2009, 41, 22–26. [CrossRef]
20. Berg, A.T.; Levy, S.R.; Testa, F.M.; D’Souza, R. Remission of Epilepsy after 2 Drug Failures in Children: A Prospective Study. Ann. Neurol. 2009, 65, 510–519. [CrossRef]
21. Thiesen, S.; Conroy, E.J.; Bellis, J.R.; Bracken, L.E.; Mannix, H.L.; Bird, K.A.; Duncan, J.C.; Cresswell, L.; Kirkham, J.J.; Peak, M.; et al. Incidence, Characteristics and Risk Factors of Adverse Drug Reactions in Hospitalized Children—A Prospective Observational Cohort Study of 6601 Admissions. BMC Med. 2013, 11, 237. [CrossRef]
22. Pal, A.; Prusty, S.; Sahu, P.; Trupti, S. Drug Utilization Pattern of Antiepileptic Drugs: A Pharmacoepidemiologic and Pharmacovigilance Study in a Tertiary Teaching Hospital in India. Asian J. Pharm. Clin. Res. 2011, 4, 96–99.
23. Yeager, K.A.; Ditiorio, C.; Shafer, P.O.; McCarty, F.; Letz, R.; Henry, T.; Schomer, D.L. The Complexity of Treatments for Persons with Epilepsy. Epilepsy Behav. 2005, 7, 679–686. [CrossRef] [PubMed]
24. Baker, G.A.; Jacoby, A.; Buck, D.; Stalgis, C.; Monnet, D. Quality of Life of People with Epilepsy: A European Study. Epilepsia 1997, 38, 353–362. [CrossRef] [PubMed]
25. Bansal, D.; Azad, C.; Kaur, M.; Rudroju, N.; Vepa, P.; Guglani, V. Adverse Effects of Antiepileptic Drugs in North Indian Pediatric Outpatients. Clin. Neuropharmacol. 2013, 36, 107–113. [CrossRef] [PubMed]
26. Isojärvi, J.I.T.; Taubøll, E.; Herzog, A.G. Effect of Antiepileptic Drugs on Reproductive Endocrine Function in Individuals with Epilepsy. CNS Drugs 2005, 19, 207–223. [CrossRef]
27. Caplan, R.; Siddarth, P.; Gurbani, S.; Hanson, R.; Sankar, R.; Shields, W.D. Depression and Anxiety Disorders in Pediatric Epilepsy. Epilepsia 2005, 46, 720–730. [CrossRef]
28. Jackson, M.J.; Turkington, D. Depression and Anxiety in Epilepsy. J. Neurol. Neurosurg. Psychiatry 2005, 76 (Suppl. S1), i45–i47. [CrossRef]
29. Jones, J.E.; Hermann, B.P.; Woodard, J.L.; Barry, J.J.; Gilliam, F.; Kanner, A.M.; Meador, K.J. Screening for Major Depression in Epilepsy with Common Self-Report Depression Inventories. Epilepsia 2005, 46, 731–735. [CrossRef]
30. Kanner, A.M. Depression in Epilepsy: A Frequently Neglected Multifaceted Disorder. Epilepsy Behav. 2003, 4 (Suppl. S4), 11–19. [CrossRef]