REVIEW ARTICLE

Factors in Determining Seizure Control in Pediatric Patients On Antiepileptic Medication: A Review of the Literature

Anaanthan Bhuvanendran Pillai[1,2] and Azmi Mohd Tamil[1]

[1]Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia.
[2]Department of Pharmacy, Hospital Tuanku Ja'afar, Seremban, Negeri Sembilan, Malaysia.

**For reprint and all correspondence: Azmi Mohd Tamil, Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Center, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Batu 9 Cheras, Kuala Lumpur, Malaysia*.
Email: drtamil@ppukm.ukm.edu.my

ABSTRACT

Received 16 August 2019
Accepted 23 August 2020

Introduction Pediatric epilepsy is one of the common illness in children. Pediatric epilepsy has significant impact not only to the patient, but also to the care takers. Furthermore, the disease could potentially cause strain in the limited resources of the healthcare system which is preventable.

Methods A search was conducted to review relevant published studies on factors affecting seizure control using PubMed/MEDLINE, Google Scholar and also Science Direct searching engines databases using keywords: paediatric seizure, seizure control, side effects, antiepileptic, adherence and quality of life.

Results In this review, we found that many factors contribute to the pediatric epilepsy, namely; compliance, genetic, age, socioeconomic factors, parental health literacy and numbers and side effects of the medications. Furthermore, there is certain factors that need to be explored in the future, such as unaddressed parental concern on treatment/medication, denial of disease and drug-drug interactions.

Conclusions Factors that had been identified can be used in the prevention and control programs, while factors which is less studied should be further studied in the future.

Keywords Paediatric seizure - seizure control - side effects - antiepileptic - factors - adherence - quality of life.

INTRODUCTION

Epidemiology

Epilepsy is one of the most common neurological non-communicable disease affecting approximately 50 million people worldwide, of all age categories.[1] One of the subgroups of population affected by epilepsy is children. In a population-based study around the world, incidence rates of epilepsy in childhood range from approximately 0.5 to 8 per 1000 person-years.[2,3,4,5] By studying the factors that contribute to the general control of seizure and the prevalence of disease, it will be very helpful to perform control and prevention activities in respect of child epidemiology.

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizure and by the neurobiological, cognitive, psychological and social and social consequences of the disease. For a person to have epilepsy, he or she should have at least one epileptic seizure. Epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in brain.[6]

The epidemiology of epilepsy however, differs for children. For instance, the etiology of pediatric epilepsy maybe idiopathic, genetic, and more commonly due to cerebral malformation especially neuronal migrational disorder. Strokes and tumors which may cause epilepsy in adults are uncommon etiology in pediatric patients. [7]

Health Care Resources

An Australian study finds that although the rate of total hospitalization due to pediatric epilepsy is lower than pediatric asthma, the cost of treatment of pediatric epilepsy will be more than treating pediatric asthma.[8] Findings from Malaysian research suggest that, the cost of medication for pediatric epilepsy is high. Mean monthly cost for monotherapy was RM 24.00 while for the polytherapy is RM 45.40. [9] Therefore, understanding the disease response towards treatment would be beneficial for the healthcare workers providing treatments and other stakeholders associated with the healthcare.

Response to seizure treatment

The response rate towards antiepileptic treatment is generally quoted between 60-70%. Although the etiology and mechanism of epilepsy disease may differ between adult and children population, the response rate are the same. Local data on the response of antiepileptic in children is very limited. Study by both Hasan et al and Ibrahim et al both suggest seizure control rate of the pediatric epilepsy patient is 70%. However, it should be noted that both studies were conducted in Penang General Hospital's Pediatric Clinic albeit 5 years apart. Another point that need to be taken into account is that the studies define seizure control in pediatric patients as fit-free for 2 months and does not follow according the International League against Epilepsy. Seizure control is defined as seizure free for 12 months after therapy. [10]

Definition of Response to the treatment/ Seizure Control

For the purpose of defining the seizure control, we referred definition from International League Against Seizure. The response rate and definition of seizure free is same for adult and children:

- The definition of response to treatment is no seizure for at least 12 months or freedom from seizures or 3 times pre-intervention inter-seizure interval (determined from seizures occurring within 12 months), whichever longer.[10]

For patients who had epilepsy surgery, the definition of seizure control would be freedom of seizure after 12 months of surgery.[11]

- Drug resistant epilepsy may be defined as failure of adequate trials of 2 tolerated and appropriately chosen and used antiepileptic schedules (either monotherapy or combination) to achieve sustained seizure freedom.[10]

Thus, we can say that period of 12 months of seizure free period as well controlled seizure.

Implication of non-responders towards treatment

Pediatric seizure affects not only the life of the child, but also the life of the parents. Larson and colleagues reported, household with child affected by epilepsy tends to have both the child and the parents sleep deprived. Furthermore, the author found the severity of the epilepsy correlates positively with the both child's and parent's sleeping dysfunction and parental fatigue. [12] Epilepsy also may cause self-perceived stigma among the patient and this may reduce the self-confidence of the person according to a cross-sectional study done in Tehran, although the author believes the level of stigma may differ from region to region.[13] And finally, as all other chronic illness, pediatric epilepsy does affect the family of the child monetarily. The cost burden not only limited to the cost to the health system (such as drugs, hospitalization, family physician visit etc.) but also cost to the individuals and households (out of pocket cost and cost associated with treatment) and indirect cost (unemployment and loss of income). A meta-analysis by Allers and colleagues (which includes pediatric epilepsy) shows epilepsy does pose substantial economic burden to the individuals and the family member .[14]

Antiepileptic drugs

Generally antiepileptic can be separated into two groups based on the drug developmental era; which is the first-generation antiepileptic and second-generation antiepileptic. The first-generation antiepileptic is any drugs licenced for treatment of epilepsy before 1980. [15] Examples that commonly used in Ministry of Health hospitals is Phenytoin, Valproate, Carbamazepine and other benzodiazepines. The problems usually faced with older generation antiepileptic is the enzyme inducing and inhibiting properties, which in turn potentially can put them in situation where interaction will occur with other medications. [15]

The newer antiepileptic used is lamotrigine, oxcarbazepine, topiramate, gabapentin, felbamate, vigabatrin, levatiracetam, zonisamide, and tiagabine. All the new and old generation of antiepileptic's efficacy have been proven in trials, although some of the trials is quasi-experimental. [16,17] The efficacy newer generation antiepileptic is not greater than the time-proven remaining old generation antiepileptic. This even can be noticed in the prescribing pattern of antiepileptic where the old generation antiepileptic still predominates. The newer generation however, possess certain advantage such as different mechanism which enable synergetic combination (in view of old generation antiepileptic have troublesome interaction). Furthermore, the newer antiepileptic has the advantage of lesser congenital malformation. [18]

This review aimed to look at factors that could contribute to control of seizure in pediatric patients.

METHODS

Search for the literature is done using databases such as PubMed, Science direct, google scholar and Scopus for journals, conference proceedings, and systematic reviews related to seizure control in pediatric patients on antiepileptic.

The scope of review was factors related to seizure control among pediatric populations taking antiepileptic medications. The criteria for this review was published articles from 1997 to 2017.

The following keywords was being used such as "seizure control factors AND pediatric patients", "seizure control factors AND children OR adolescents", "seizure response rate factors AND pediatric patients" were used to identify the relevant journals via the databases.

All the journals were screened titles and if were appropriate were reviewed the abstracts. The full text of the selected articles was retrieved if were in English. A total of 33 articles includes original articles and reviews were obtained for the purpose of this review.

RESULTS

A total of 29 literature has been extracted for the literature search. We could divide the factors that affect seizure control into three domains, namely; sociodemographic factors, medication related factors, and genetic factors. Sociodemographic domains can be factors such as age, gender, familial income and parental health literacy. On the other hand, medication domain can factor such as noncompliance and or number of antiepileptics. The final domain that we found is the genetic domain. Both medication domain and sociodemographic status domain contribute the most (each 12 studies) of the literature. Certain studies do describe more than one domain as affecting seizure control such as genetic and medication or sociodemographic status and medication. The result of the search can be summarized in Table 1.

Table 1 Characteristics of study of factors affecting seizure control in pediatric population

No	Author	Title	Year	Study Design	Domain
1	McPherson et al	Noncompliance with medical follow-up after pediatric intensive care.	2002	Cohort	Medication
2	Zorc et al	Predictors of primary care follow-up after a pediatric emergency visit for asthma	2005	Randomized Control Trial	Medication
3	Paula Gardiner & Dvorkin, L	Promoting Medication Adherence in Children	2006	Practice statement	Medication
4	McCormick et al	Emotional functioning, barriers, and medication adherence in pediatric transplant recipients	2013	Cross Sectional Study	Medication
5	Hovinga CA et al	Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians.	2008	Cross Sectional Study	Medication
6	Scheffer IE et al	Epilepsy genetics revolutionizes clinical practice.	2014	Narrative review	Genetic

7	Lin WH et al	Seizure control through genetic and pharmacological manipulation of Pumilio in Drosophila: a key component of neuronal homeostasis.	2017	Narrative review	Genetic
8	Shorvon S et al	Oxford textbook of epilepsy and epileptic seizures.	2012	Textbook Chapter	Genetic
9	Wirrel EC	Treatment of Dravet Syndrome	2016	Narrative review	Genetic
10	Malik MA et al	Predictors of intractable childhood epilepsy.	2008	Cross Sectional Study	SD status & Genetic
11	Berkovic SF	Genetics of Epilepsy in Clinical Practice.	2015	Narrative review	Genetic
12	Holmes GL	Epilepsy in the developing brain: lessons from the laboratory and clinic. Epilepsia.	1997	Narrative review	SD status
13	Wyllie E	Developmental aspects of seizure semiology: problems in identifying localized-onset seizures in infants and children	1995	Narrative review	SD status
14	Poudel P	Predictors of poor seizure control in children managed at a tertiary care hospital of Eastern Nepal	2016	Cross Sectional Study	SD status & Medication
15	Berg AT	Predictors of intractable epilepsy in childhood: a case-control study	1996	Case-control study	SD status
16	Wirrell E	Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: A retrospective, population-based study.	2012	Cohort	SD status
17	Christensen J	Gender differences in epilepsy	2005	Cross Sectional Study	Gender
18	Begley C	Socioeconomic status, health care use, and outcomes: persistence of disparities over time.	2011	Cohort	SD status
19	Paschal AM	Parent health literacy and adherence-related outcomes in children with epilepsy.	2016	Cross Sectional Study	SD status & Medication
20	Sanders LM	Literacy and child health: a systematic review.	2009	Systematic Review	SD status
21	DeWalt DA	Health literacy and child health outcomes: a systematic review of the literature.	2009	Systematic Review	SD status
22	Getnet A,	Antiepileptic drug nonadherence and its predictors among people with epilepsy.	2016	Cross Sectional Study	Medication
23	Canevini MP	Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy	2010	Cross Sectional Study	Medication
24	Hasan SS	Antiepileptic drug utilisation and seizure outcome among paediatric patients in a Malaysian public hospital.	2010	Cohort	Medication
25	Conn KM	Parental beliefs about medications and medication adherence among urban children with asthma.	2005	Cross Sectional Study	SD Status
26	Conn KM	The impact of parents' medication beliefs on asthma management.	2007	Cross Sectional Study	SD Status

27	Patsalos PN	The importance of drug interactions in epilepsy therapy	2002	Narrative Review	Medication
28	Buchanan N	Medications which may lower seizure threshold	2001	Narrative Review	Medication
29	Lalic M	Lamotrigine and valproate pharmacokinetics interactions in epileptic patients.	2009	Randomised Control Trial	Medication

SD status = Sociodemographic status

Sociodemographic domains

Age

The child's brain when immature is the state where its more susceptible to seizures than mature brains (adult).[30] This statement can be understood by observation that, incidence of seizure is highest when the child affected is in the early years of life. However, this subsequently reduces as the child ages.[30] This phenomenon can be explained from the animal studies; immature animals have lower seizure threshold compared with matured animals. In such animals, inhibitory systems are lacked compared to excitatory system.[30]

The manifestations of seizure symptoms are influenced by the age. Children with temporal lobe epilepsy the age of 6 years old and older tend to have presentation which is similar to adult, (auras, activity arrest, simple and complex automatisms, and dystonic posture) while younger child tend to have less complex behaviour. [31]

Irrespective of the type of seizure, most of the child (60%) will eventually outgrow their epilepsy and discontinue the antiepileptic. [7,31] Such patients will be treated with medication up to 2 years of fit-free, similar with the adult patients. However, there are intractable childhood epilepsy that have poor prognosis. Uncontrolled seizure may lead to mental retardation, difficulty in learning and behavioural problem. [7]

Furthermore, the treatment with antiepileptic for child may differ from adults in term of effect.[7] For example, age has influence of the pharmacokinetics of the antiepileptic. Neonates commonly will eliminate antiepileptic slower than other age group. After neonatal stage, as the child grow up, the clearance of antiepileptic drug tends to be faster and have wide intra-group variability.[7] Antiepileptic drugs tend to be more harmful to the immature brain compared to the matured brain. Studies demonstrated that antiepileptic affect cognitive and behavioural disturbances in children. The adverse effects may continue despite discontinuation of the drug. [30]

Poudel and colleagues finds that younger age onset of seizure have poor seizure control.[32] The same finding was also echoed by Berg and colleagues through a case control study identifying predictors of medically treated intractable epilepsy. In the study Berg and colleagues found that cases have significantly lower age compared to control with the odds ratio of 10.42, p=0.03 .[33] Furthermore, Berg and colleagues found the risk of getting intractable pediatric epilepsy decreases by age with odds ratio of 0.77 with p- value less than 0.0001. Similar finding also evident in the case-control study by Malik and colleagues where seizure at infancy has the odds ratio 5.27.[28]

Gender

In our literature search, we could not find any significant association for gender and seizure control. Interestingly Malik and colleagues found there is association, where being male, increases the odd by 3.92.[28] However, the author agrees that there are conflicting findings about gender effect on the seizure control in other sources. For instance, Wirrell and colleagues does not find any statistically significant association of gender with seizure control. [34] The gender however does have a difference in susceptibility in developing certain epilepsy subtype. [35]

Socioeconomic

Socioeconomic factors have an important role in disease outcome. Any shortcoming in socioeconomic factors must be identified to promote social equity. In a study by Begley and colleagues, they found out that general epilepsy patient's population from lower socioeconomic strata have higher rate of hospitalization and emergency department visit. The population also tend to experience greater like hood of getting uncontrolled seizure, drug related side effects, stigmatized and have poor quality of life.[36]

As for the pediatric seizure, the same outcome could be expected as socioeconomic of adult parents will affect the child. Iqbal and colleagues conducted a study examining the effect of parental education on the quality of life and general health of epilepsy children. The shows parental education, plays a significant role in general health and overall quality of life of the epileptic child.[37]

Another component of socioeconomic factor is household income. Adequate house hold income reflects adequate quality of life. A study by Paschal and colleagues found that household income is a predictor for less miss dose. [38]

Parental health literacy

Parental health literacy plays an important point in seizure control. Since most epileptic child will be

taken care by the parents, it is vital for the parents to have an adequate health literacy to provide better care for their offspring. In a study by Paschal and colleagues, it was noted that, parent's health literacy has an overall predictor for miss dose and seizure frequency .[38] However, it must be noted the seizure frequency in Paschal et al serves just as an arbitrary marker as the investigator just asked about the seizure frequency in last 30 days and not as the definition by International League Against Epilepsy.[10]

In a systematic review by sanders and colleagues, caregiver with low health literacy have association with poor preventative behavior and poor child health outcome. Furthermore, adults with poor health literacy has 1.2 to 4 times tendency to exhibit behaviors that promotes bad outcome on child's health.[39]

Similar findings were found in another systematic review by DeWalt and Hink, that parents with low literacy generally have low health knowledge and had bad behavior that were less advantageous for children compared with parents with high literacy. [40]

Medication-Related Domain

1) Noncompliance

Noncompliance can be divided into 2 categories: noncompliance toward treatment and noncompliance towards follow up. In a study by McPherson and colleagues, in a cohort of 111 patients who discharged from pediatric PICU, was found that the probabilities of being non-compliance is increasing by the number of appointments.[19] This finding is very significant for child epilepsy as the child is expected to be seen in neurology clinic for quite a long-time till can be weaned off from medication (if permissible). And the compliance towards the follow up is critically depends on the parent's commitment. In another study by Zorc and colleagues, after ED visit for pediatric asthma, only 55% of the patients went to the primary healthcare provider. The factors that affect the decision of parents going to the follow-up is lack of convenience, long hour waiting at primary healthcare provider clinic, and "perceived severity" of illness. [20] To date, there is still no studies that examines the association of follow-up and epilepsy control.

Poor adherence to medications is common in chronic illness (epilepsy, cystic fibrosis, asthma, diabetes).[21] McCormick King and colleagues suggest from their study, among the barriers towards their pediatric subjects and parents towards adherence to medication is hassle in life, stress and common family conflict [22]. In a study by Hovinga and colleagues, the level of adherence in all epilepsy patient taking medication is 71% with 29% nonadherence. The study reported the seizure control was 64% and 27% respectively.[23] Thus, compliance play role in seizure control.

2) Polytherapy

For most of the epilepsy treatment, monotherapy will be used to start treatment. In the study of medically intractable pediatric seizure patient in Nepal, polytherapy is associated with poor seizure control .[32] The same pattern can be observed in Hassan and colleagues' study in Penang, where pediatric patient with polytherapy is associated with poor seizure control.[44]

3) Side effect of antiepileptics

In a cross-sectional study by Getnet and colleagues, the odds ratio of a person who experience side effects of epilepsy to be noncompliant to medication is 1.70 and probably the commonest reason to stop medication without consulting doctor. [41]

However, the probability of patient getting side effects is based on individual susceptibility rather than number of antiepileptics. [42]

A study in Malaysia shows that HLA-B*1502 is strongly associated with Carbamazepine-induced Toxic Epidermal Necrosis/Steven Johnson Syndrome in the Malay population in Malaysia, as already been demonstrated in Han Chinese in Taiwan. [43] However, there is no local study linking side effects and non-compliance of the antiepileptics.

Genetic Domain

The Field of epilepsy genetic has seen many developments since the discovery of the first epilepsy gene in the last 22 years ago .[24] As we already discussed about the seizure control in pediatric is 60-70%, roughly one third of those who do not respond to treatment can be attributed to the genetic cause. [25] For instance, the well-known genetic cause of the genetic influence of pediatric seizure is Dravet syndrome which begin after 6 months .[26] Dravet syndrome unlike other epilepsy syndrome can only be treated by Clobazam, Valproate, and Topiramate. [27]

Genetic factor by itself can predict the likelihood of family members to develop epilepsy. For instant if one has Genetic Generalized Epilepsy (GGE), his or her first-degree family members have 8 times more risk of developing the disease compared to general population .[24] However, in a case control of Malik and colleagues, it was noted that family history does not statistically predict the odds of having intractable seizure .[28.] These findings may imply that a precise genetic marker need to be established from blood test to predict the like hood of getting intractable epilepsy rather than just asking for family history. As we already discussed before, the etiology of seizure may differ in adult population with child, thus more detailed history has to be asked to determine the genetic effect in our population.

With all the advances in the field of epileptic genetic, targeted therapy may be expected to be trending and may lead to the development of novel therapies in years to come. [29]

DISCUSSION

From this review of literature, we can say that there are few areas of research which has been well studied in other pediatric diseases such as childhood asthma but not in pediatric epilepsy. The areas that need further research in pediatric epilepsy is unaddressed parental concern on the treatment of antiepileptic, parental belief on medication, and effect of drug-drug interactions**.** These factors can play a critical role in ensuring compliance in treatment.

In a study by Conn and colleagues, 67 asthmatic children's (on controller medication) parents were interviewed. Only 22% of the parents is completely complaint while 34% of the parents were having strong concern about the medication (fear of unknown medication side effects). The parents with strong concern about the medication was associated with poor compliance towards the medication. [45] In another study by Conn and colleagues 2 years later, this time to assess parental the effect of perception necessity versus concern on the medication. Surprisingly the study shows parents with necessity index higher than concern, tend to give better compliance results than otherwise. [46]

Parental concerns should be addressed clearly during prescribing or dispensing medication to prevent noncompliance. For instance, the parents could stop giving medication for chronic illness if he/she felt the patient is well (in this case stop medication when not fitting) to reduce the like hood to get adverse drug effects. [21]

The drug-drug interactions in epilepsy regimes may have both beneficial or harmful effect. The beneficial effects would lead to enhancing therapeutic potential. On the other hand, the harmful effect will be increase in adverse effect or reduced efficacy. [50] This effect is more prominent in old generation antiepileptic due to enzyme inducing and inhibiting effects. Other than antiepileptic itself, there are other medications that could potentially reduce seizure threshold, increasing the chance of the patient to get seizure. Medications such as propofol, certain antibiotics (penicillin, cephalosporin, imipenem, amphotericin), and clozapine. [51]

Among the group of patients particularly vulnerable to the drug interactions in epilepsy is those with genetic polymorphism, elderly, children, and pregnancy. The child especially is vulnerable because they can metabolize drugs faster than adults. Certain medication such as lamotrigine have high inter-individual variability depending of the age of child and co-administered antiepileptic .[50] Lamotrigine's metabolism can be inhibited by valproate, thus increasing serum level of lamotrigine. [52] This may potentiate the side effect of getting serious rash that leads to hospitalization (Steven Johnson syndrome). The monitoring of blood level of lamotrigine is not possible in Malaysia, due to unavailable reagent for therapeutic drug monitoring.

Interestingly, we found that the factors are not mutually exclusive. For example, study by study by Paschal and colleagues, it was noted that, parent's health literacy has an overall predictor for miss dose and seizure frequency. Furthermore, study by Paudel shows that polytherapy is associated with poor seizure control as well. The reason maybe high pill burden leads to noncompliance. Thus, for future study, researchers should keep into consideration of these possible confounding effects of the factors.

CONCLUSION

Pediatric seizure control is contributed by many factors. Further studies should be done to ascertain factors which is less studied. Factors such as unaddressed parental concern on the treatment of antiepileptic/parental belief on medication, denial of the disease on the epilepsy treatment, and effect of drug-drug interactions is less studied on the control of seizure in pediatric.

REFERENCES

1. Epilepsy. Fact Sheet [Internet].: World Health Organization; 2019 Available from: https://www.who.int/news-room/fact-sheets/detail/epilepsy.
2. Aaberg KM, Gunnes N, Bakken IJ, Søraas CL, Berntsen A, Magnus P, Lossius MI, Stoltenberg C, Chin R, Surén P. Incidence and prevalence of childhood epilepsy: a nationwide cohort study. Pediatrics. 2017 May 1;139(5): e20163908.
3. Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. Epilepsia. 1991 Aug;32(4): 429-45.
4. Oka E, Ohtsuka Y, Yoshinaga H, Murakami N, Kobayashi K, Ogino T. Prevalence of childhood epilepsy and distribution of epileptic syndromes: a population-based survey in Okayama, Japan. Epilepsia. 2006 Mar;47(3):626-30.
5. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics. 2012 Feb 1;129(2):256-64.
6. Fisher RS, Boas WV, Blume W, Elger C, Genton P, Lee P, Engel Jr J. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005 Apr;46(4):470-2.

7. Malaysian society of Neurosciences: Epilepsy Council. Consensus Guideline on The Management of Epilepsy 2017. Available from: http://www.neuro.org.my/MSN_GUIDELINE/MSN_GUIDELINE_Consensus%20Guidelines%20on%20the%20Management%20of%20Epilepsy%202017.pdf.
8. Bellon ML, Barton C, McCaffrey N, Parker D, Hutchinson C. Seizure-related hospital admissions, readmissions and costs: Comparisons with asthma and diabetes in South Australia. Seizure. 2017 Aug 1; 50:73-9.
9. Ibrahim MI, Ismail HI, Seng TB. The use of lamotrigine and other antiepileptic drugs in paediatric patients at a Malaysian hospital. Pharmacy World and Science. 2005 Oct 1;27(5):403-6.
10. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77.
11. Commission on Neurosurgery of the International League Against Epilepsy (ILAE) 1997–2001:, Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, Sperling MR, Lüders H, Pedley TA. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia. 2001 Feb 8;42(2):282-6.
12. Larson AM, Ryther RC, Jennesson M, Geffrey AL, Bruno PL, Anagnos CJ, Shoeb AH, Thibert RL, Thiele EA. Impact of pediatric epilepsy on sleep patterns and behaviors in children and parents. Epilepsia. 2012 Jul;53(7):1162-9.
13. Ghanean H, Jacobsson L, Nojomy M. Self-perception of stigma in persons with epilepsy in Tehran, Iran. Epilepsy & Behavior. 2013 Aug 1;28(2):163-7.
14. Allers K, Essue BM, Hackett ML, Muhunthan J, Anderson CS, Pickles K, Scheibe F, Jan S. The Economic Impact of Epilepsy: A Systematic Review. BMC neurology. 2015 Dec;15(1):245.
15. Koubeissi MZ, Azar NJ, editors. Epilepsy Board Review: A Comprehensive Guide. Springer; 2017 Jun 27. P. 213-233.
16. Friedman D, French JA. Clinical trials for therapeutic assessment of antiepileptic drugs in the 21st century: obstacles and solutions. The Lancet Neurology. 2012 Sep 1;11(9):827-34.
17. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia. 2001 Apr 20;42(4): 515-24.
18. Lee SK. Old versus new: why do we need new antiepileptic drugs? Journal of epilepsy research. 2014 Dec;4(2):39.
19. McPherson ML, Lairson DR, Smith EB, Brody BA, Jefferson LS. Noncompliance with medical follow-up after pediatric intensive care. Pediatrics. 2002 Jun 1;109(6): e94-.
20. Zorc JJ, Scarfone RJ, Li Y. Predictors of primary care follow-up after a pediatric emergency visit for asthma. Journal of Asthma. 2005 Jan 1;42(7):571-6.
21. Paula Gardiner & Dvorkin L. Promoting Medication Adherence in Children. American Family Physician. 2006; 74 (5): 793-798.
22. McCormick King ML, Mee LL, Gutiérrez-Colina AM, Eaton CK, Lee JL, Blount RL. Emotional functioning, barriers, and medication adherence in pediatric transplant recipients. Journal of Pediatric Psychology. 2013 Sep 28;39(3):283-93.
23. Hovinga CA, Asato MR, Manjunath R, Wheless JW, Phelps SJ, Sheth RD, Pina-Garza JE, Zingaro WM, Haskins LS. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians. Epilepsy & Behavior. 2008 Aug 1;13(2):316-22.
24. Scheffer IE. Epilepsy genetics revolutionizes clinical practice. Neuropediatrics. 2014 Apr;45(02):070-4.
25. Lin WH, Giachello CN, Baines RA. Seizure control through genetic and pharmacological manipulation of Pumilio in Drosophila: a key component of neuronal homeostasis. Disease models & mechanisms. 2017 Feb 1;10(2):141-50.
26. Shorvon S, Guerrini R, Cook M, Lhatoo S, editors. Oxford textbook of epilepsy and epileptic seizures. OUP Oxford; 2012 Dec 20.
27. Wirrell EC. Treatment of Dravet syndrome. Canadian Journal of Neurological Sciences. 2016 Jun;43(S3):P.13-8.
28. Malik MA, Hamid MH, Ahmed TM, Ali Q. Predictors of intractable childhood epilepsy. J Coll Physicians Surg Pak. 2008 Mar 1;18(3):158-62.
29. Berkovic SF. Genetics of Epilepsy in Clinical Practice: Genetics of Epilepsy in Clinical Practice. Epilepsy currents. 2015 Jul;15(4):192-6.

30. Holmes GL. Epilepsy in the developing brain: lessons from the laboratory and clinic. Epilepsia. 1997 Jan;38(1):12-30.
31. Wyllie E. Developmental aspects of seizure semiology: problems in identifying localized-onset seizures in infants and children. Epilepsia. 1995 Dec;36(12):1170-2.
32. Poudel P, Chitlangia M, Pokharel R. Predictors of poor seizure control in children managed at a tertiary care hospital of Eastern Nepal. Iranian journal of child neurology. 2016;10(3):48.
33. Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: a case-control study. Epilepsia. 1996 Jan;37(1):24-30.
34. Wirrell E, Wong-Kisiel L, Mandrekar J, Nickels K. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: A retrospective, population-based study. Epilepsia. 2012 Sep;53(9):1563-9.
35. Christensen J, Kjeldsen MJ, Andersen H, Friis ML, Sidenius P. Gender differences in epilepsy. Epilepsia. 2005 Jun;46(6):956-60.
36. Begley C, Basu R, Lairson D, Reynolds T, Dubinsky S, Newmark M, Barnwell F, Hauser A, Hesdorffer D. Socioeconomic status, health care use, and outcomes: persistence of disparities over time. Epilepsia. 2011 May;52(5):957-64.
37. Begley C, Basu R, Lairson D, Reynolds T, Dubinsky S, Newmark M, Barnwell F, Hauser A, Hesdorffer D. Socioeconomic status, health care use, and outcomes: persistence of disparities over time. Epilepsia. 2011 May;52(5):957-64.
38. Paschal AM, Mitchell QP, Wilroy JD, Hawley SR, Mitchell JB. Parent health literacy and adherence-related outcomes in children with epilepsy. Epilepsy & Behavior. 2016 Mar 1;56:73-82.
39. Sanders LM, Federico S, Klass P, Abrams MA, Dreyer B. Literacy and child health: a systematic review. Archives of Pediatrics & Adolescent Medicine. 2009 Feb 2;163(2):131-40.
40. DeWalt DA, Hink A. Health literacy and child health outcomes: a systematic review of the literature. Pediatrics. 2009 Nov 1;124(Supplement 3): 265-74.
41. Getnet A, Woldeyohannes SM, Bekana L, Mekonen T, Fekadu W, Menberu M, Yimer S, Assaye A, Belete A, Belete H. Antiepileptic drug nonadherence and its predictors among people with epilepsy. Behavioural neurology. 2016;2016.
42. Canevini MP, De Sarro G, Galimberti CA, Gatti G, Licchetta L, Malerba A, Muscas G, La Neve A, Striano P, Perucca E, SOPHIE Study Group. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. Epilepsia. 2010 May;51(5):797-804.
43. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B* 1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens–Johnson syndrome in the multi-ethnic Malaysian population. International Journal Of Dermatology. 2011 Feb;50(2):221-4.
44. Hasan SS, Bahari MB, Babar ZU, Ganesan V. Antiepileptic drug utilisation and seizure outcome among paediatric patients in a Malaysian public hospital. Singapore Medical Journal. 2010 Jan 1;51(1):21.
45. Conn KM, Halterman JS, Fisher SG, Yoos HL, Chin NP, Szilagyi PG. Parental beliefs about medications and medication adherence among urban children with asthma. Ambulatory Pediatrics. 2005 Sep 1;5(5):306-10.
46. Conn KM, Halterman JS, Lynch K, Cabana MD. The impact of parents' medication beliefs on asthma management. Pediatrics. 2007 Sep 1;120(3):e521-6.
47. Garay-Sevilla ME, Malacara JM, Gutiérrez-Roa A, Gonzalez E. Denial of disease in type 2 diabetes mellitus: its influence on metabolic control and associated factors. Diabetic Medicine. 1999 Mar;16(3):238-44.
48. Gavin AT, Fitzpatrick D, Middleton RJ, Coleman MP. Patients' denial of disease may pose difficulty for achieving informed consent. Bmj. 2002 Apr 20;324(7343):974.
49. Levine J, Warrenburg S, Kerns R, Schwartz G, Delaney R, Fontana A, Gradman A, Smith S, Allen S, Cascione R. The role of denial in recovery from coronary heart disease. Psychosomatic Medicine. 1987 Mar.
50. Patsalos PN, Fröscher W, Pisani F, Van Rijn CM. The importance of drug interactions in epilepsy therapy. Epilepsia. 2002 Apr;43(4):365-85.
51. Buchanan N. Medications which may lower seizure threshold. Australian Prescriber. 2001 Feb;24(1):8-9.
52. Lalic M, Cvejic J, Popovic J, Bozic K, Golocorbin-Kon S, Al-Salami H, Mikov M. Lamotrigine and valproate pharmacokinetics interactions in epileptic patients. European Journal Of Drug

Metabolism And Pharmacokinetics. 2009 Jun 1;34(2):93-9.