Determination of healthcare resource and cost implications of using alternative sodium valproate formulations in the treatment of epilepsy in children in England: a retrospective database review

Hannah Batchelor

1. *Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, United Kingdom*
   hannah.batchelor@strath.ac.uk

Abstract

Objectives: The aim of this study was to compare the adherence, healthcare resource and cost implications of using Episenta® minitablets or Epilim® monolithic tablet in the treatment of epilepsy in children in England.

Design: This is a retrospective analysis of healthcare administrative databases

Setting: The study analysed data collected from Primary Care (Clinical Practice Research Datalink (CPRD)) and Secondary Care (Hospital Episode Statistics (HES)) in England, UK

Participants: Patients (stratified by age 0-12; 0-17 and 18+ years) with a diagnosis of epilepsy in receipt of a new prescription for Episenta® minitablets or Epilim® monolithic tablet from January 2012 to October 2017. Limited to those with a minimum of 12 months follow-up

Main outcome measures: Determining the impact of sodium valproate formulation on measures of treatment adherence and healthcare resource usage.

Results: There were 793 patients in the dataset: 84 on Episenta® minitablets and 709 on Epilim® tablets. Measures of medication adherence were not significantly different between the minitablet formulation and the monolithic matrix tablet. However there was a greater annualised incidence rate of epilepsy related primary healthcare contacts in a paediatric population from the tablet formulation compared to those treated with minitablets (95% CI [-1.561,0.0152]) for those aged 0-12 and (95% CI [-1.3234,-0.0058]) for those aged 0-17. This is found despite a lower dose being used in the minitablet cohort (595mg vs 945 mg for the tablet) for those aged 0-17 which indicates effective therapy at a lower dose using the minitablet compared to the monolithic tablet formulation.

Conclusions: Minitablet formulations of sodium valproate (presented as granules in capsules or sachets) can provide better therapeutic outcomes and reduced associated healthcare resource costs compared to monolithic tablets in children and young people with epilepsy. The interpretation of this data is limited by the large difference in sample size between the two groups which needs additional investigation to generate matched data for future comparisons. Further work is required to understand why the Episenta® minitablets formulation generated better outcomes in paediatric populations.

Keywords: sodium valproate; epilepsy; age-appropriate formulation; minitablet; adherence; healthcare costs

INTRODUCTION

The use of age-appropriate formulations that are acceptable to use, provide adequate adherence and appropriate therapy is a critical objective for patients, healthcare regulators and the pharmaceutical industry. Epilepsy is a neurological disorder that affects 1 in every 200 children [1]. There are many pharmacological agents used in the treatment of epilepsy. Oral antiepileptic drugs are the mainstay of treatment for those affected where sodium valproate is the most frequently prescribed anti-epileptic in paediatric populations [2].

Adherence to antiepileptic medicines is essential to minimise seizures; improve symptom management and quality of life [3]. Poor adherence to epilepsy medication has been reported in children with estimates of adherence ranging from 30-70 % [4]. Low adherence may be implicated in poor seizure control in some patients leading to increased interactions with healthcare services; previous studies have demonstrated that non-adherence is associated with increased morbidity and mortality [4].

Measuring adherence to medication is complicated with the gold standard measurement being direct electronic monitoring of medication. Secondary measures of adherence include medicines reconciliation; self-recorded adherence (eg patient diaries) and pharmacy dispensing records [5]. Medication possession ratio (MPR) compares the percentage of medication collected by the patient that has been prescribed; however scores over 100% are possible when patients collect medication early. The proportion of days covered (PDC) removes the possibility of having an adherence measure greater than 100% as it normalises the data for the time scale.

Taste and child refusal were reported to be the most frequent barriers to medicines adherence in a recent study in children aged 2-12 years [6]. Difficulties in swallowing tablets was also listed as a barrier in the same study [6]. Age-appropriate formulations have the potential to improve adherence and therapeutic outcomes for children. Previous research compared a sprinkle formulation (Depakote) to valproic acid syrup (Depakene) in twelve children with epilepsy aged from 5-16 years; the sprinkle was preferred by parents and children due to ease of administration and palatability, respectively. Furthermore there were fewer fluctuations in serum concentrations with the sprinkle compared to the syrup [7]. Another study compared the acceptance of a sodium valproate prolonged release microgranule to a liquid product in 199 children; the results showed that refusal to take the medicine decreased upon switching to the microgranule (Micropakine®LP; MPK) as did the frequency that parents were using rewards [8]. Furthermore more stable plasma profiles as well as fewer seizures were experienced in children using the microgranule compared to the liquid formulation [8].

Sustained release multi-unit valproate formulations have been linked with reduced fluctuations in plasma drug concentrations leading to improved tolerability and superior compliance [9]. Sodium valproate granules that provide modified-release with superior taste to the liquid were introduced in 2006 with the Chronosphere® formulation (by Sanofi-Aventis, France) and with the Episenta® mini tablets (from Desitin Pharmaceuticals GmbH) approved by the MHRA in 2006 and available to prescribe from March 2007 for children aged over 6 years. Alternative sustained release valproate formulations include monolithic tablets that are supplied as a single unit with instructions not to crush or chew each tablet.

The aim of this study was to conduct a retrospective database review to investigate the relationship between prescribing and medicines possession as well as clinical outcomes for two formulations of sodium valproate to provide insights into whether an age-appropriate minitablet formulation (Episenta®) provides better healthcare outcomes (and associated reduced costs) compared to a conventional monolithic tablet (Epilim® Chrono) in children with epilepsy. The Episenta® mini tablets are available in unit doses of 150mg or 300mg within a capsule or at 500mg or 1000mg within a sachet (where each minitablet has an approximate mass of 3mg). The Epilim® Chrono tablet is available in unit doses of 200, 300 or 500 mg.

METHODS

Main data source and extracted data

Anonymised and pseudonymised linked datasets covering primary care and secondary care were used. Primary Care data was sourced from the Clinical Practice Research Datalink (CPRD) and Secondary Care data sourced from Hospital Episode Statistics (HES) data. The protocol is provided in the supplementary file.

The data collected included:

- Proportion of Days Covered (PDC) – (total days all drug(s) available/days in follow-up period).
- Medication Possession Ratio (MPR) – (total Rx days of supply/last Rx date – first Rx date + last Rx days of supply).
- Time to switch/discontinuation (days) – discontinuation will be said to have occurred when any gap between valproate prescriptions exceeds a maximum allowable gap duration (MAGD) of (1.5 x the number of days supply of the last prescription).

- Incidence rate and annualised tariff cost ppy of overall emergency admission– assessed only in HES eligible patients applying current payment-by-results tariff [10] to the Health Resource Group allocation for the admission.
- Incidence rate of epilepsy-related emergency admission – assessed only in HES eligible patients.
- Incidence rate of overall Outpatient contacts – assessed only in HES eligible patients.
- Incidence rate and annualised estimated cost per patient per year (ppy) of overall primary healthcare care professional contacts– derived by applying published costs for units of Healthcare [11].
- Incidence rate of epilepsy related primary healthcare care professional contacts – where the consultation includes a Read code related to epilepsy.
- Annualised total primary care medication costs per patient per year (ppy) observed – derived by applying electronic Drug Tariff costs to prescriptions issued during observation period [12].

The study covered patients from January 2012 to October 2017 for patients with a minimum of 12 months follow-up in the dataset.

Cohort Profile

The inclusion criteria for patients were:

1. A new prescription of Episenta® minitablets or Epilim® monolithic tablet, i.e. no previous prescription of any controlled release sodium valproate in their data
2. A diagnosis of epilepsy based on read codes in their health record

The exclusion criteria for patients were:

1. The diagnosis or symptomatic manifestation of bipolar disorder or manic episodes, to ensure that the use of sodium valproate is mainly for epilepsy
2. Contraindications for sodium valproate as specified in the summary of product characteristics published by NICE, to ensure that patients analysed will be receiving sodium valproate appropriately

Activity during pregnancy or birth will not be included in calculations, although the patients themselves will not be excluded from the cohort. This is because birth or maternity activity and their attendant costs, may not be attributable to specific medications. Additionally, sodium valproate is contraindicated during pregnancy unless there is no suitable alternative treatment, and is

contraindicated in girls and women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.

Sub-cohorts of patients based on age were constructed, giving us groups of ages 0-12, 0-17 and 18+. This was performed given the natural differences in dosing, dose response and epilepsy in these age groups. The 0-12 group was selected as the general consensus is that from the age of 12 young people can use of tablets and the data may be anticipated to be equivalent to that of adults [13]. The actual paediatric population, defined as those from 0-17 was also included as an additional comparator to those over 18 (there is overlap in the 0-12 and 0-17 age groups).

Analysis

The following parameters were calculated:

Medication possession ratio

$$\frac{1}{N}\sum_{i=1}^{N}\left(\frac{sum\ of\ all\ qty\ in\ observation\ period\ where\ cohort\ drug\ appears\ for\ patient\ i}{number\ of\ days\ in\ observation\ period\ for\ patient\ i}\right)$$

N= number of patients

Assumption: all patients (adult and children) take at least one unit (tablet or sachet/capsule) a day.

Switch Rate:

$$\frac{\begin{array}{c}Prescription\ of\ a\ different\ epileptic\ drug\ after\ the\ date\ cohort\ drug\ prescribed\\ AND\ No\ prescription\ of\ cohort\ drug\ after\ the\ date:\\ First\ day\ cohort\ drug\ prescribed + [1.5 * (quantity)] - 1\}\end{array}}{Total\ Number\ of\ patients\ in\ the\ Cohort}$$

Assumption: all patients (adult and children) take at least one unit (tablet or sachet/capsule) a day.

Discontinuation Rate:

$$\frac{\begin{array}{c}No\ prescription\ of\ cohort\ drug\ after\ the\ date:\\ First\ day\ cohort\ drug\ prescribed + [1.5 * (quantity)] - 1\}\end{array}}{Total\ Number\ of\ patients\ in\ the\ Cohort}$$

Assumption: all patients (adult and children) take at least one unit (tablet or sachet/capsule) per day.

Statistical analysis

Model specification was developed using manual forward-inclusion with testing of all two-way interactions. The non-inferiority margin was assessed by converting the odds ratio (OR) for Episenta® vs. Epilim® Chrono group membership to relative risk (RR) using the following formula: RR = OR / (1 – p + (p x OR)) where p is the observed risk in the reference group (Epilim® Chrono)

RESULTS

In total, there were 793 patients in the dataset, with 84 on Episenta® minitablets (62% male) and 709 on Epilim® monolithic tablets (67% male) . The demographics and resulting data are shown in Table 1.

		Population details					
		0-12 years		**0-17 years**		**18+ years**	
		Episenta® minitablets	**Epilim® Chrono**	**Episenta® minitablets**	**Epilim® Chrono**	**Episenta® minitablets**	**Epilim® Chrono**
Primary care	Number in population	19	67	30	125	54	584
	Medication Possession Ratio (MPR)	3.41	2.80	3.74	2.78	4.15	3.91
	Switch rate	15.79%	2.99%	16.67%	3.20%	70.37%	4.97%
	Discontinuation rate	57.89%	37.31%	53.33%	37.60%	64.81%	48.29%
	Average daily dose (mg)	504.92	961.28	595.27	944.67	850.96	1,077.65
	Mean prescription length (days)	45.71	36.48	45.58	38.62	14.53	31.39
	Number of prescriptions per patient per year*	7.62	12.89	9.14	11.20	17.30	13.39
	Annualised incidence rate of overall primary healthcare care professional contacts	14.53	23.27	20.04	20.54	39.35	35.83
	Annualised incidence rate of epilepsy related primary healthcare care	0.00	0.77	0.06	0.72	0.87	1.08

	professional contacts						
	Annualised estimated cost of incidence rate of overall primary healthcare care professional contacts per patient year	£523.10	£837.59	£721.34	£739.47	£1,416.69	£1,289.86
Secondary Care	Number in population	19	67	30	125	54	584
	Annualised incidence rate of overall emergency admissions per patient	0.00	0.39	0.06	0.23	0.61	0.74
	Annualised incidence rate of overall emergency admissions for epilepsy per patient	0.00	0.21	0.06	0.13	0.39	0.61
	Annualised emergency 30 day readmissions per patient	0.00	0.20	0.00	0.11	0.00	0.19
	Annualised emergency 30-90 day readmissions per patient	0.00	0.36	0.02	0.19	0.22	0.16

*excludes patients with less than 30 days in cohort

Table 1. Data used within this study. Primary Care data was sourced from the Clinical Practice Research Datalink (CPRD) and Secondary Care data sourced from Hospital Episode Statistics (HES) data.

Comparison of prescribing rate of products

The data reveals that the monolithic tablets are prescribed more frequently compared to the minitablets in all cohorts; this is despite the Epilim Chrono® monolithic matrix tablet being more than 10mm in length which is larger than many tablets deemed suitable for children [15]. The large

difference in prescribing rates has resulted in unequal sample groups which can affect statistical power and Type I error rates [16]. The data did not permit investigation into the reasons that underpin the difference in prescribing rates although previous research has highlighted that previous exposure to a medicine and its past clinical success have a big role in prescribing decisions [17]. This may explain the greater use of the older, established product (Epilim Chrono® monolithic matrix tablet) in this cohort. The prices of the products are similar: 30x 300mg Epilim Chrono® monolithic matrix tablets have an NHS indicative price of £5.24 (17.5p per unit) whereas the Episenta 300mg modified-release capsules have an indicative price of £13.00 for 100 units (13p per unit) [18].

Measures of medication adherence

Measures of medication adherence were not significantly different between the Episenta® minitablet formulation and the Epilim® monolithic matrix tablet with MPR >1 and PDC values being >100% for both products. However, differences were noted in the switch rate with rates of 16% for the Episenta® minitablet formulation and 3% for the Epilim® monolithic matrix tablet in the 0-12 group (95% CI [0.9383, 39.5751]) and with 70 % compared to 5% (95% CI [22.7244, 90.9127]) in the 18+ cohort. This switch rate suggests that a higher proportion of patients were being switched from the Episenta® minitablet formulation compared to the Epilim® monolithic tablet in all ages although the reasons for this are not clear. The discontinuation rate is linked to the switch rate and thus higher discontinuation rates were observed for the minitablets compared to the monolithic tablet yet these differences were not statistically significant 95% CI [0.8193, 6.5133] in the 0-12 year cohort and 95% CI [0.8493, 4.2355] in the 0-17 years cohort. The discontinuation rates reported here are higher than those previously reported (~30%) for valproic acid [19].

Measures of dose and prescription length

The average dose was lower for the Episenta® minitablet formulation compared to the Epilim® monolithic tablet showing significantly lower doses in both paediatric sub-cohorts 505 vs 961 mg, 95% CI [-631.88, -280.83] for 0-12 years and 595 vs 945 mg, 95% CI [-503.06, -195.73] for 0-17 years. In paediatric populations the mean prescription length of the minitablets was somewhat longer yet this was not statistically different. The number of prescriptions per patient year is related to the mean prescription length where patients on the Episenta® minitablets were receiving fewer prescriptions per year yet each was covering a longer length of time.

Measures of primary care healthcare costs

There was a higher incidence of primary healthcare contacts for those on the Epilim® monolithic tablet compared to the minitablets in the sub-cohort aged 0-12 years (23.27 vs 14.53) whereas the incidence was similar for those in the 0-17 and 18+ cohorts. When this was focussed on the annualised incidence rate of epilepsy related primary healthcare contacts there was a higher rate from the Epilim® monolithic tablet population compared to those treated with Episenta® minitablets as shown in Figure 1. Furthermore the annual costs per patient of those contacts for patients on Episenta® minitablets were statistically significantly lower in the 0-12 (£523 vs £838; 95% CI [-329.4446, -299.5317]) and 0-17 sub-cohorts (£721 vs £739; 95% CI [-29.2872, -6.9779]).

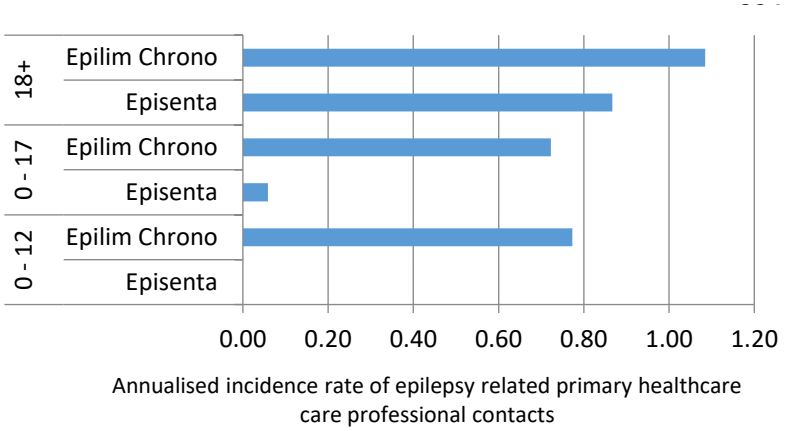

Figure 1. Comparison of rate of epilepsy interactions with primary care HCPs based on formulation prescribed. Note that the p values were 0.058 for those aged 0-12; 0.050 for those aged 0-17 and 0.43 for those aged 18+.

Measures of secondary care healthcare interactions

A reduction in the overall and epilepsy-related emergency admissions per patient annually in the Episenta® minitablet group was identified compared to the Epilim® monolithic tablet group; however these differences were not statistically significant. In terms of readmissions, there was also a reduction in the 30-day and 90-day readmissions in the Episenta® minitablet group compared to Epilim® monolithic tablet group.

DISCUSSION

This data set (Table 1) has shown several benefits of using an age-appropriate minitablet formulation compared to a monolithic tablet in children and young people with epilepsy. Although some data reached statistical significance other trends were observed without reaching statistical significance yet the sizes of the differences and the consistency of findings across the sub-cohorts suggests that these trends will likely hold in a study with a larger population and longer follow-up time. However, there is a need to further understand the higher switch rates and discontinuation of the minitablet formulation.

The fact that the benefits in the Episenta® group were identified despite having a lower average daily dose (on average 47.5% less in the 0-12 year and 37% less in the 13-17 year old sub-cohorts on the Episenta® minitablet formulation) are of great interest. The lower dose has cost benefits to the healthcare service not only in medication costs but from these data also from healthcare associated costs. Effective therapy from any medication requires a balance of risk versus benefit; this is particularly meaningful for sodium valproate that has well documented risks including teratogenicity where the lowest effective dose should be used for females with childbearing potential [20]. In all therapy the lowest effective dose should be the target for all patients.

Previous studies on enteric coated formulations have reported benefits including rapid emptying into the small intestine which provides superior protection from the gastric environment; faster drug dissolution and absorption; and quicker onset of action for multiparticulate formulations compared to single unit tablets [21, 22]. It is worth noting that these studies have been conducted in adults and little is known on the gastrointestinal transit of multiparticulate formulations in children [23]. Evaluation of prolonged release dosage forms in paediatric populations is complex as the majority of biopharmaceutics assessments are undertaken in adult populations or using *in vitro* apparatus that has been designed to mimic adult anatomy and physiology [24]. The two formulations used within this study differ in the manner in which they control the release of the drug. Epilim® monolithic tablets use an inert matrix core (containing hypromellose, ethylcellulose, and hydrated Silica) where diffusion of water into the matrix will control the rate of drug release from the tablet; it is essential that this core is not crushed or split as this will lead to immediate release of the drug and potential toxicity. The instructions for use state that the tablets should be swallowed whole and not crushed or chewed [25]. The Episenta® minitablet formulation uses a coating (made of ethylcellulose with the plasticizer dibutyl sebacate) to control the rate of drug release from each minitablet; if the coating is damaged the drug will be released rapidly yet the presence of multiple units (a 300mg

capsule contains approximately 100 units) means that toxicity is unlikely. Chewing of minitablets has been reported in previous studies with rates of 36-50% in those under 3 years of age [26] rates are not available for older children or adults; however it is unlikely that all minitablets administered would be chewed upon administration of the Episenta® formulation. Drug absorption occurs to the greatest extent within the small intestine; thus the rate of drug absorption will depend not only on the mechanisms built into the formulations but also the rate at which the formulations reach the small intestine. Previous work has demonstrated that small units (pellets or minitablets) reach the small intestine more rapidly than single large units (tablets) [27]; yet other work has contradicted this finding [28]. However, in both studies a single tablet of >3mm was used. Other studies on multiple units have reported that granules transit through the GI tract in a more reproducible way compared to tablets [29]; this results in reduced plasma drug fluctuations. These alternative types of formulation are distinguished in the EMA Guideline on quality of modified release products; this document goes on to state that the development of single unit non-disintegrating dosage forms for use in children is discouraged as their residence time in the stomach is unpredictable and a higher risk of dose-dumping and/or erratic concentration profiles [30].

This difference in the formulation attributes is likely to underpin the superiority observed for the Episenta® minitablet formulation as a less erratic concentration profile is achieved which provides better therapeutic outcomes at the lower dose in the paediatric cohorts.

Strengths and limitations

Use of the Clinical Practice Research Datalink and National Health Service Digital Hospital Episode Statistics databases allowed access to a large national pool of patients diagnosed with epilepsy. Data was captured over a period of 5 years providing a larger data set than has previously been reported.

However a weakness of this study is that, while the medication possession ratio provides a reliable measurement of prescriptions provided, this may not translate into an equally reliable measurement of true adherence. Generation of an electronic prescription does not ensure that medication is taken and this measure may overestimate true adherence. There is also no information on whether patients received a supply of medicine from other sources such as hospital pharmacies although this would likely to be a small fraction. The adherence rates of 100% reported from this data set are higher than values reported in other research on antiepileptic medicines in children [4]. However, as the objective of this work is to compare two formulations the impact on true adherence is likely to be similar for both products thus comparison of outcomes is still valid.

The lack of balance in the population sizes also provides complications in interpretation of the data as the uneven population sizes for the two cohorts (Episenta® minitablets and Epilim® monolithic tablets) makes statistical significance harder to attain. The reason behind the difference in prescribing rates for the two products is unknown.

The CPRD primary care database contains the anonymised, longitudinal medical records of patients registered with contributing primary care practices across the UK. CPRD contains patient registration information, and all care events that general practice staff record yet prescriptions are not directly linked to a specific diagnosis. In this study indication of use of sodium valproate was inferred using patient clinical diagnosis and referral records. Hospital Episode Statistics (HES) is a database containing details of all admissions, A and E attendances and outpatient appointments at NHS hospitals in England. The nature of the data from CPRD and HES is that it is prone to incomplete or incorrect medical records and coding, lack of specificity, and captures prescriptions but not prescription fills. However, there is precedent of use of this type of data in similar research studies. As the objective of this work is to compare two formulations the impact of these limitations is likely to be similar for both products thus comparison of outcomes is still valid. Further work is required to understand why the minitablet valproate formulation generated better outcomes in children and young people compared to a conventional tablet.

CONCLUSION

There is a clear trend showing lower healthcare costs (measured by a reduction in the incidence rate of contact with primary and secondary care healthcare professionals) per patient annually using an age-appropriate Episenta® minitablet formulation compared to the conventional monolithic tablet. This was found despite the lower dose being used in this cohort which indicates effective therapy at a lower dose using the minitablet compared to the monolithic tablet formulation.

Information about the risks of valproate use in girls and women of childbearing age and the prevent programme toolkit can be found on the following website:
https://www.gov.uk/guidance/valproate-use-by-women-and-girls.

Acknowledgements

This study was produced through a research collaboration between Health iQ and the Department of Primary Care and Public Health, Imperial College London. This study was implemented based on the protocol 18_003R2, which was approved by ISAC, the screening committee of the Clinical Research Practice Data Link and is compliant with the guidelines of the MHRA and NHS Digital, as well as the laws, policies and rules surrounding information governance in the UK and the EU.

This research was funded by Desitin Pharma Ltd.

Competing interests: The author declares financial support for the submitted work from Desitin Pharma Ltd.; HKB has done consultancy for Desitin Pharma Ltd

Author Contribution statement

Hannah Batchelor interpreted and analysed the data and drafted the manuscript.

Patient consent for publication: Not required

Data availability statement: The data used in this study were provided by Desitin Pharma Ltd as a result of a collaboration between Health iQ and the Department of Primary Care and Public Health, Imperial College London. Individuals who would like to request access to the data should contact the corresponding author where reasonable requests will be granted access.

References

1. Russ, S.A., K. Larson, and N. Halfon, *A national profile of childhood epilepsy and seizure disorder.* Pediatrics, 2012. **129**(2): p. 256-64.
2. Egunsola, O., I. Choonara, and H.M. Sammons, *Anti-epileptic drug utilisation in paediatrics: a systematic review.* BMJ Paediatrics Open, 2017. **1**(1): p. e000088.
3. Jones, R.M., et al., *Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs.* Seizure, 2006. **15**(7): p. 504-8.
4. Shetty, J., et al., *Adherence to antiepileptic drugs in children with epilepsy in a Scottish population cohort.* Dev Med Child Neurol, 2016. **58**(5): p. 469-74.
5. Farmer, K.C., *Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice.* Clinical Therapeutics, 1999. **21**(6): p. 1074-1090.
6. Gutierrez-Colina, A.M., et al., *Adherence barriers in pediatric epilepsy: From toddlers to young adults.* Epilepsy & Behavior, 2018. **80**: p. 229-234.
7. Cloyd, J.C., et al., *Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance, and preference.* The Journal of Pediatrics, 1992. **120**(4 PART 1): p. 634-638.
8. Motte, J., et al., *Acceptabilité et tolérance du valproate de sodium, granules à libération prolongée, en monothérapie chez l'enfant épileptique à partir de trois ans.* Archives de Pédiatrie, 2005. **12**(10): p. 1533-1539.
9. Bergmann, A., et al., *Epilepsietherapie mit retardierter Valproinsäure - Erfahrungen mit 1172 Patienten.* Akt Neurol, 1999. **26**(03): p. 121-126.
10. England, N., *National Tariff Payment System.* https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015, 2014-2015.
11. Curtis, L., *Unit Costs of Health and Social Care 2014.* Personal Social Services Research Unit, University of Kent, Canterbury, 2014. **https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2014/?file=full**.
12. Wales, N.E.a., *Electronic Drug Tariff.* http://www.ppa.org.uk/edt/September_2014/mindex.htm, 2014.
13. EMA, *Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use* EMA/CHMP/QWP/180157/2011 2011. **https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-pharmaceutical-development-medicines-paediatric-use_en-0.pdf**.
14. Grant, R.L., *Converting an odds ratio to a range of plausible relative risks for better communication of research findings.* BMJ : British Medical Journal, 2014. **348**: p. f7450.
15. van Riet-Nales, D.A., et al., *Oral medicines for children in the European paediatric investigation plans.* PLoS One, 2014. **9**(6): p. e98348.
16. Rusticus, S.A. and C.Y. Lovato, *Impact of Sample Size and Variability on the Power and Type I Error Rates of Equivalence Tests: A Simulation Study,.* Practical Assessment, Research, and Evaluation, 2014. **19**(11).
17. Davari, M., E. Khorasani, and B.M. Tigabu, *Factors Influencing Prescribing Decisions of Physicians: A Review.* Ethiopian journal of health sciences, 2018. **28**(6): p. 795-804.
18. Committee, P.F., *BNF for Children (online).* London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. **<http://www.medicinescomplete.com> [Accessed on [20-10-2020]]**.
19. Dudley, R.W., S.J. Penney, and D.J. Buckley, *First-drug treatment failures in children newly diagnosed with epilepsy.* Pediatr Neurol, 2009. **40**(2): p. 71-7.
20. Tomson, T. and D. Battino, *Pregnancy and epilepsy: what should we tell our patients?* J Neurol, 2009. **256**(6): p. 856-62.

21. Thyssen, A., et al., *Pharmacokinetics of rabeprazole granules versus tablets, and the effect of food on the pharmacokinetics of rabeprazole granules in healthy adults—cross-study comparison.* Clinical Pharmacology in Drug Development, 2014. **3**(5): p. 406-416.
22. Tirpude, R.N. and P.K. Puranik, *Rabeprazole sodium delayed-release multiparticulates: Effect of enteric coating layers on product performance.* Journal of advanced pharmaceutical technology & research, 2011. **2**(3): p. 184-191.
23. Bowles, A., et al., *Specific aspects of gastro-intestinal transit in children for drug delivery design.* International Journal of Pharmaceutics, 2010. **395**(1): p. 37-43.
24. Batchelor, H.K., et al., *Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients.* European Journal of Pharmaceutics and Biopharmaceutics, 2013. **85**(3, Part B): p. 833-842.
25. Sanofi, *Epilim Chrono 300mg Controlled Release Tablets.* Available at: https://www.medicines.org.uk/emc/product/3987/smpc#gref (accessed 20-10-20).
26. Kluk, A., et al., *Can preschool-aged children swallow several minitablets at a time? Results from a clinical pilot study.* Int J Pharm, 2015. **485**(1-2): p. 1-6.
27. Davis, S., J. Hardy, and J. Fara, *Transit of pharmaceutical dosage forms through the small intestine.* Gut, 1986. **27**(8): p. 886-892.
28. Podczeck, F., et al., *Gastrointestinal transit of model mini-tablet controlled release oral dosage forms in fasted human volunteers.* J Pharm Pharmacol, 2007. **59**(7): p. 941-5.
29. Stefan, H. and B. Fraunberger, *[Valproate sustained release in the treatment of epilepsy].* Fortschr Neurol Psychiatr, 2005. **73**(11): p. 681-6.
30. EMA, *Guideline on quality of modified release products.* https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-oral-modified-release-products_en.pdf, 2014.