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# The Efficacy and Tolerability of Levetiracetam as a First Line Monotherapy in Childhood Epilepsy

A. Connolly[1,2], M. Quirke[2], S. Crowley[3], E. Hayes[4], C. Hurley[4], M. Keegan[5], G. Griffin[5], D. Webb[1,5]

1. Children's Neurology Service, CHI@Tallaght, Tallaght University Hospital, Tallaght, Dublin 24
2. Trinity Centre for Practice and Healthcare Innovation, Trinity College Dublin, 24 D'Olier street, Dublin 2
3. Children's Neurology Service, CHI@Temple St, Temple St, Dublin 1
4. Children's Neurology Service, Cork University Hospital, Cork
5. Children's Neurology Service CHI@Crumlin, Crumlin, Dublin 12

**Abstract**

***Introduction***
To examine efficacy and tolerability of Levetiracetam monotherapy as a first line agent in a national cohort of children with epilepsy, naïve to anti-epileptic medication.

***Methods***
A retrospective analysis of children with epilepsy who attended 4 Irish tertiary Paediatric Neurology Clinics (2009-2015) started on Levetiracetam as a first line monotherapy.

***Results***
182 children were identified aged one month to 16 years (mean 6.2 years (SD=5.1) Retention at 6 and 12 months was 88% (n=161) and 83% (n=145) respectively. 75% (n=104) achieved seizure freedom or > 50% improvement in seizure control at 12 months. 30% (n=55) experienced ≥1 adverse effect with aggression (12%; n=21) the most frequent. Treatment was discontinued in 16% (n=29) because of intolerance. Underlying conditions and epilepsy type were not found to influence efficacy or tolerability.

***Conclusion***
Levetiracetam monotherapy was observed as effective and safe for children with epilepsy although side effects limit tolerance in a sizeable minority.

## Introduction

Epilepsy in childhood frequently presents as a significant challenge to treatment. The decision to choose a specific antiepileptic drug (AED) as the first drug in any child is based on the age profile, gender, seizure types and EEG findings balanced with the perceived efficacy of the drug, its safety profile and impact on behaviour and existing co-morbidities. Levetiracetam has been proven to be effective in controlling seizures, with a favourable safety profile in adults and children over the age of 16 years as both an adjunctive and a monotherapy[1], and as an adjunctive therapy for children under the age of 16 years[2,3,4].

Two recent systematic reviews report that since Levetiracetam received a license for adjunctive use in childhood epilepsy in 2005 there has been widespread use of Levetiracetam as an initial monotherapy in children. This is despite insufficient evidence to confirm its effectiveness as an initial monotherapy in childhood epilepsy[6,7].

There is strong evidence to support the use of Levetiracetam in adults and as an adjunctive treatment for children. Positive outcomes with these populations have supported its use as monotherapy in childhood epilepsy despite a deficit in published evidence in this cohort. While Sodium Valproate is considered a very effective option it is not recommended for use in females[5]. Alternatives to Levetiracetam such as Oxcarbazepine and Lamotrigine are available. However, more favourable cognitive outcomes with Levetiracetam have supported it use in this population[1].

A study published since this review, identified 231 children from a single hospital in Turkey over a 10-year period, who were prescribed Levetiracetam as monotherapy and found that Levetiracetam was effective in treating this group[8]. It would seem important that clinicians continue to report experiences with this medication.

In the current study, the findings are presented from the first national evaluation of Levetiracetam, focusing on efficacy and tolerability, in a group of Irish children with epilepsy who were naïve to AEDs and who were prescribed Levetiracetam as monotherapy.

## Methods

The aim of this study was to assess (i) the efficacy; (ii) tolerability of Levetiracetam as monotherapy in a national sample of children with a diagnosis of epilepsy and; (iii) to evaluate patient variables that might influence efficacy and tolerability. The children included were 16 years or younger with a diagnosis of epilepsy who were naïve to medication and had been started on Levetiracetam as a first line monotherapy between January 2009 and December 2015.

All the children were attending a Consultant Paediatric Neurologist and had a diagnosis of epilepsy based on history and EEG findings. The EEGs were all interpreted by a Consultant Neurophysiologist. Seizure semiology and epilepsy syndrome were based on International League Against Epilepsy (ILAE) guidelines. The presence of an underlying condition was based on review by a Consultant Paediatric Neurologist (motor impairment), formal evaluation by a Paediatric Neuro-psychologist (cognitive impairment) and review by a Child Psychiatrist (ADHD and ASD). Levetiracetam was commenced at 10mg/kg/day in two divided doses and increased typically to 20-60mg/kg/day over a period of 8-10 weeks. Parents (and children where appropriate) were informed of potential side effects of Levetiracetam prior to starting treatment. Parents and children were asked to keep careful seizure and side effect diaries and patients were reviewed at 6-month intervals.

An audit of medical records was undertaken across all four acute Tertiary Paediatric Hospital sites in the Republic of Ireland. Total population sampling was employed. An audit tool was designed by the research team. The tool included age, gender, co morbidities as well as seizure and treatment history. It was piloted on one site (n=10). No other identifying information was gathered and only data previously collected as part of patient usual care was included. Prior to data collection, a letter informing families of the study, was sent to all those who met the inclusion criteria, by the on-site clinical staff involved in the study. The audit was completed by on-site clinical staff who worked directly with the medical records involved. Anonymised data was gathered at each hospital site using the questionnaire. This data was cleaned by the Principal Investigator (PI) in collaboration with the on-site collaborator and then entered onto SPSS. Ethical approval was granted by each of the four Hospital Ethics Committees and approval to conduct the study was granted by Hospital Management. A condition of approval was that the sample would be pooled together to minimise identification of hospital sites and thus individual patients.

In total, n=182 patients from across the four sites were included. Given the nature of the data type there was some missing data. Where information pertaining to a variable was missing, this case was excluded from analysis. Data was analysed using SPSS (version 23). A range of descriptive and inferential tests (T-tests, chi analysis, Fisher's exact tests, Kruskal-Wallis test) were used to profile the sample, identify the efficacy levels, type the prevalence of tolerability issues and identify possible predictors of efficacy and tolerability with $p < 0.05$ considered significant.

## Results

*Patient Profile and Co-morbidities*

A multi-site chart review identified information on 182 patients prescribed Levetiracetam during a seven-year period (January 01st 2009-December 31st 2015) (Table 1). The mean age was 6.2 years (SD=5.1) ranging one month - 16 years and 62% (n=113) were female. Almost half of the sample (49%; n=89) experienced generalised epilepsy while 44%

(n=80) had focal epilepsy and 7% (n=13) experienced both. Co-morbidities were reported in 44% (n=80) of the group and cognitive impairment was the most common (79%; n=63) (Table 1).

| **Table 1. Patient profile (n=182 unless otherwise stated)** | |
|---|---|
| **Age** | |
| Mean | 6.2 years (SD=5.1) |
| Median | 4 years |
| Range | 1 month to 16 years |
| | **% (n)** |
| <2 years | 25% (46) |
| 2-7 years | 34% (62) |
| 8-11 years | 18% (33) |
| 12-16 years | 23% (41) |
| **Gender** | |
| Female | 62% (113) |
| Male | 38% (69) |
| **Seizure semiology** | |
| Focal only | 44% (80) |
| Generalised only | 49% (89) |
| Both focal and generalised | 7% (13) |
| **Epilepsy Syndrome (n=176*)** | |
| Idiopathic | 56% (98) |
| Symptomatic | 28% (49) |
| Cryptogenic | 17% (29) |
| **Co-morbidities (n=80**)** | |
| One or more | 44% (80) |
| Cognitive impairment | 79% (63) |
| Motor impairment | 51% (41) |
| ASD | 23% (18) |
| Behavioural | 18% (14) |
| ADHD | 4% (3) |
| *ES data inconclusive (n=5) or missing (n=1).<br>**Some patients experienced more than one comorbidity | |

*Retention Rate*

The retention rate at 6 months was 88% (n=161). Retention data at 12 months was available for n=175 (i.e. observation period was less than 12 months for n=7) and a retention rate of 83% (n=145) was recorded. Of the 17% (n=30) who discontinued by 12 months, the median length of time on treatment was 3.7 months. The most frequently cited reason for discontinuation was adverse effects (60%; n=18) followed by insufficient improvement (20%; n=6) or both (13%; n= 4).

*Efficacy of Levetiracetam*

Treatment was continued to at least 12 months in N=145 patients. Of these patients, efficacy of Levetiracetam, in terms of seizure control was available for n=139 patients (n=3 non-compliant, n=3 data missing), Table 2. Improvement in seizure control by one year was recorded in 75% (n=104), of which 54% (n=75) reported seizure freedom for at least 6 months and 21% (n=29) reported >50% seizure reduction (Table 2).

Further analysis revealed that boys were significantly more likely to report seizure freedom (of at least 6 months) than girls (68% versus 45%, $p<0.05$) and, whilst younger children reported a higher response rate (i.e. freedom or reduction versus no improvement), Kruskal-Wallis analysis found no significant difference between response rate and age. Epilepsy type, seizure semiology, seizure frequency pre-treatment or presence of an underlying condition did not significantly contribute to response rate for this group (Table 2).

| Table 2. Patient profiles and response to Levetiracetam at 12 months (n=139) | | | | | |
|---|---|---|---|---|---|
| **Variable (n)** | **Response rate (139)** | | | | |
| | **Seizure free > 6 months (75/139)** | **> 50% Seizure reduction (29/139)** | **No improvement (35/139)** | **Test score** | **p** |
| **Age (138) (median)** | 3 years | 3 years | 5 years | 0.87[1] | >0.05 |
| **Gender (139)** | **% (n)** | **% (n)** | **% (n)** | | |
| Female (85) | 45% (38) | 25% (21) | 31% (26) | N/A[2] | **<0.05*** |
| Male (54) | 68% (37) | 15% (8) | 17% (9) | | |
| **Seizure Semiology (139)** | | | | | |
| Focal (63) | 54% (34) | 22% (14) | 24% (15) | N/A[2] | >0.05 |
| Generalised (64) | 53% (34) | 20% (13) | 27% (17) | | |
| Both (12) | 58% (7) | 17% (2) | 25% (3) | | |
| **Underlying condition present (139)** | | | | | |
| Yes (63) | 46% (29) | 27% (17) | 27% (17) | N/A[2] | >0.05 |
| No (76) | 61% (46) | 16% (12) | 24% (18) | | |
| [1] Kruskal-Wallis test<br>[2] Fishers exact test, score not produced<br>*Significant<br>N/A Not applicable | | | | | |

*Tolerability of Levetiracetam (n=182)*

At least one adverse effect was experienced during treatment in 30% of patients (n=55). The most commonly reported were aggression (12%; n=21) and low mood (10%; n=18) followed by irritability (8%; n=15). In total, 16% (n=29) stopped Levetiracetam medication due to side effects and the majority of this group (76%, n=22) discontinued within 12 months (Median=4 months). Amongst this group who stopped, nearly half (48%; n=14) experienced aggression, 38% (n=11) a low mood and 35% (n=10) irritability (Table 3).

| Table 3. Adverse effects (A/E) of Levetiracetam (n=182) | | |
|---|---|---|
| | **% (n)** | |
| **Any A/E reported** | 30% (55) | |
| **A/E and drug withdrawal*** | 16% (29) | |
| | **Study population (n=182)** | **Drug withdrawal due to A/E* (n=29)** |
| **Two or more side effects** | 13% (23) | 55% (16) |
| **Breakdown of adverse effects reported** | | |
| **Aggression** | 12% (21) | 48% (14) |
| **Low mood** | 10% (18) | 38% (11) |
| **Irritability** | 8% (15) | 35% (0) |
| **Tiredness/Somnolence** | 6% (10) | 17% (5) |
| **Anxiety** | 3% (5) | 17% (5) |
| **Insomnia** | 3% (5) | 3% (1) |
| **Depression** | 2% (3) | 7% (2) |
| **Inattention** | 2% (3) | 7% (2) |
| **Attempted suicide** | 2% (3) | 7% (2) |
| **Self-harm** | 1% (2) | 3% (1) |
| **Poor appetite** | 1% (1) | 3% (1) |
| **Weight gain** | 1% (1) | 3% (1) |
| **Dizziness** | 1% (1) | 0% (0) |
| **Rash** | 1% (1) | 3% (1) |
| **Hallucinations** | 1% (1) | 0% (0) |
| * Patients in whom drug withdrawal was primarily due to drug side effects | | |

Those who discontinued Levetiracetam due to adverse effects were significantly more likely to have experienced two or more adverse effects (55% versus 45%; p<0.001). Children who experienced adverse effects were significantly older (Median=8 years) than those who did not (Median=3 years; p<0.005). No other association between adverse effects and patient profile were observed (Table 4).

**Table 4: Adverse effects and patient profile (n=182)**

| | **Adverse effects** | | | |
|---|---|---|---|---|
| **Category** | **Yes (55)** | **No (127)** | **Z** | **P** |
| **Age** | | | | |
| Median | 8 years | 3 years | 3.5[1] | **<0.005*** |
| **Gender** | **% (n)** | **% (n)** | | |
| Male | 25% (17) | 75% (52) | 1.2[2] | >0.05 |
| Female | 34% (38) | 66% (75) | | |
| **Epilepsy type** | | | | |
| Focal | 24% (19) | 76% (61) | 3.7[2] | >0.05 |
| Generalised | 34% (30) | 66% (59) | | |
| Both | 46% (6) | 54% (7) | | |
| **Seizure frequency pre-treatment** | | | | |
| <5 seizures | 29% (20) | 71% (50) | 0.2[2] | >0.05 |
| ≥5 seizures | 33% (33) | 67% (67) | | |
| **Underlying condition [3]** | | | | |
| Yes | 35% (28) | 65% (52) | 1.2[2] | >0.05 |
| No | 27% (27) | 73% (75) | | |

*Significant
[1] Mann Whitney test
[2] Chi test
[3] Note, each underlying condition from table 1 was also analysed separately with no significant association

**Discussion**

This study examined the efficacy and tolerability of Levetiracetam as initial monotherapy in a national paediatric population with epilepsy. Overall, the efficacy and tolerability of Levetiracetam in the majority of patients was well demonstrated. The observation of patients who experienced adverse effects and /or did not show improvement highlights the need for pre-treatment education and counselling for patients and their families on the limitations of AED treatment.

This study reports a patient response rate of 75% at twelve months, in children on monotherapy who were naive to AEDs. This was similar to a recent study which reported a patient response rate of 78%[8]. An international systematic review of Levetiracetam reported seizure freedom of up to 100% but also recognised that many patients represented in these figures had benign epilepsy syndromes and seizure types[6]. Several studies report a response rate of over 90%, but the higher response rate in these studies may be explained by small sample size and the benign nature of the epilepsy syndromes included[9,10].The current study provides an analysis of a large national sample of children with a broad range of epilepsy syndromes with only one patient identified as having a benign Rolandic epilepsy.

This study also indicates that males are significantly more likely to experience seizure freedom on Levetiracetam, a finding previously not reported. Like other studies, no association was found between efficacy and age, dosage or seizure type/epilepsy syndrome or underlying diagnosis[6,8]. Not surprisingly perhaps, patients who discontinued

medication did so more quickly if they had adverse effects than if they were not seeing improvements in seizure control-a finding not extrapolated in other studies to make comparisons.

Nearly a third of children were found to experience adverse effects but overall tolerability was high and no associated profile risk factors were observed. A recent study identified only 17% of children reported experiencing adverse effects and of these only a minority 14% were on monotherapy[8]. The most commonly reported adverse effects in the current study were emotional and behavioural changes, which mirrors the small number of randomised controlled trials undertaken with children on Levetiracetam[6]. More specifically, aggression and low mood are the most common reason for cessation in most studies[6,7,8] and this was also the case in the present study. Other studies identified somnolence as another common adverse effect[6,8], a finding not replicated in this study. While efficacy was not associated with age, Levetiracetam was more likely to have been tolerated by younger children but this may be related to their ability to communicate what they were experiencing.

A systematic review examining Levetiracetam as monotherapy, concluded that retention rates were considered the most appropriate method of examining tolerability[6]. The current study records a 12 month retention rate of 83%, substantially higher than the 54% reported in a similar recent study[8], and within the range reported in an international review of 57-100%. Whilst reasons for retention drop off were not provided by Tekgul and colleagues[8], we found that retention rates and reasons behind these rates vary considerably depending on the time period examined. In this study, a total of 16% of patients discontinued treatment due to adverse effects. This compares with rates ranging from 0-17% in other studies[6,7,8].

The lack of consistency across studies concerning the inclusion of patients who have underlying conditions was identified in one published systematic review[6]. Whilst the list of underlying conditions captured in the current study was not exhaustive, our study did not identify any association between having a motor or cognitive impairment and efficacy and/or tolerability. However, the small numbers limits the conclusions that can be drawn from this analysis. It is also likely that the young age and cognitive profile of a small number of this sub-group further limits their ability to clearly define adverse effects being experienced. Data on positive effects on the child other than seizure control were also not recorded.

The findings of this study add to the body of literature available by identifying the efficacy and tolerability of Levetiracetam. Considering that this drug is now outside of patent it is unlikely that further expensive randomised controlled trials will be undertaken in children. Since completion of data collection Levetiracetam has continued to be widely used as monotherapy in childhood epilepsy[11]. It is important therefore that clinicians continue to share experiences with Levetiracetam from different clinical settings so that medical staff, patients and their families are fully informed on the risks and benefits of taking this medication.

**Declaration of Conflicts of Interest:**
All authors declare no conflict of interest.

**Corresponding Author:**
Ann Connolly,
RANP Epilepsy (Childhood),
CHI@Tallaght,
Tallaght University Hospital,
Dublin 24
Email: ann.connolly03@tuh.ie

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