

## Effect of the Duration of Withdrawal of Antiepileptic Drugs on the Risk of Seizure Recurrence in Childhood Epilepsy

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### ABSTRACT

**Background:** There is no consensus on how long the duration of antiepileptic drugs (AEDs) withdrawal after seizure control should be. Some centers recommend very rapid withdrawal while others recommend prolonged tapering. **Objective:** This study was designed to identify the risk of seizure recurrence after rapid or slow discontinuation of AEDs in epileptic children who are in remission and to assess variables that may modify the risk of recurrence in rapid or slow withdrawal. **Methods:** One hundred and six epileptic children in remission were included: sixty one of them were subjected to AEDs withdrawal over six months while the remaining forty five patients underwent withdrawal of drugs over three months. All patients were followed up for one year for any new seizure occurs. **Results:** No significant statistical difference was found between both groups regarding the rate of seizure relapse in one year follow up ( $P=0.81$ ). It is found that gender, presence of family history of epilepsy, type of seizures, seizure free duration, number of drugs used and type of drugs have no effect on the relapse rate irrespective to the duration of tapering; However, abnormal EEG at withdrawal of therapy was associated with significantly higher relapse rate in the group of three months (rapid) withdrawal. **Conclusion:** It was concluded that seizure relapse in epileptic children undergoing AEDs withdrawal is not affected by the duration of tapering of treatment apart from children with abnormal EEG in remission who may experience less recurrence rate if 6 months withdrawal is adopted. [Egypt J Neurol Psychiat Neurosurg. 2010; 47(4): 593-598]

**Key Words:** epilepsy, withdrawal, AED, tapering, recurrence of epilepsy

### INTRODUCTION

Epilepsy is a major public health concern, directly affecting about 50 million people worldwide, and involving an additional 500 million people as family members and care givers of epileptic patients<sup>1</sup>.

Epilepsy is a varied disorder with variable causes e.g. idiopathic, genetic & acquired brain insults; its outcome is also heterogeneous<sup>2</sup>.

Medical management with antiepileptic drugs (AEDs) remains the first-line treatment in patients with epilepsy<sup>3</sup>. Although epilepsy is a chronic neurological condition, 60-70% of people with epilepsy become seizure free for at least 2 years and be faced with the decision to withdraw from their AEDs<sup>4</sup>. Numerous reports highlight the side effects of AEDs, such as fatigue, drowsiness and impaired cognitive function. With the emergence of evidence for the reversal of such effects following discontinuation, withdrawal decision of AEDs becomes paramount<sup>5</sup>.

There is no consensus on how long the duration of antiepileptic drug withdrawal after seizure control should be<sup>6</sup>.

Some centers recommend very rapid withdrawal of AEDs over less than six weeks<sup>7</sup>, other recommend drug withdrawal over three months<sup>8</sup>, while prolonged tapering of AEDs over six to nine months is the usual practice in many hospitals<sup>9</sup>.

#### Objectives:

1. To identify the risk of seizure recurrence after rapid (taper period of three months) or slow (taper period of six months) discontinuation of antiepileptic drugs in epileptic children in remission.
2. To clarify variables that may affect the risk of seizure recurrence in rapid and slow withdrawal of treatment.

### METHODS

The present prospective study was conducted during the period from October 2005 to July 2009. The study population was 106 children with epilepsy at Pediatric and Neurology inpatient & outpatient clinics in Zagazig University Hospitals. Epileptic seizures were defined according to the guidelines for epidemiologic research of the International League Against Epilepsy<sup>10</sup>. The epileptic children in remission had undergone either six months or three months duration for AED withdrawal.

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**Inclusion criteria:**

All children achieved remission of epilepsy (2 years or more seizure free duration) and aged 4-13 years were included in the study.

**Exclusion criteria:**

The following epileptic children were not included in the study:

- Patients underwent tapering of AEDs before 2 years seizure free duration.
- Patients dropped out during the one year follow up period.
- Patients underwent tapering of AEDs between 3-6 months.
- Patients controlled on more than 2 AEDs.
- Patients with multiple care givers.
- Patients with infantile spasms & neonatal seizures since the natural history of these conditions is unique.

The 106 cases subjected to the study were categorized into two groups according to the duration of AEDs withdrawal after two years or more seizure free period:

- \* Group I: 61 patients underwent the usual protocol of Zagazig University-Pediatric and Neurology departments of withdrawing AEDs over 6 months period by declining the drug dosage by 25% every one and half month.
- \* Group II: 45 patients underwent the withdrawal of AEDs in a period of 3 months.

The patients of group II were subjected for the three months withdrawal method by declining the dose of drugs by 25% every three weeks.

The following data were collected for all patients by direct interviewing the care givers, by telephone and by assessing the outpatient files and records of the patients:

- Age, sex and residence.
- Family history of epilepsy (considered positive if one of first degree-relatives had a history of epilepsy).
- Duration free from seizures before AED tapering.
- Type of seizures.
- Number, names and doses of AED used.
- EEG was done unless the patient had already had an EEG within one month before or after tapering.
- Follow up: Patients were followed up for one year for any new seizure occurs (as the highest rate of relapse of seizures occurs in the first 12 months of AEDs withdrawal)<sup>9,11</sup>.

**Ethical considerations:**

Permission was taken from the head of Pediatric department and the head of Neurology department before the beginning of the study. A routine consent was taken from the care givers of the sixty-one patients subjected to the six months tapering method (This consent is taken from any care giver of epileptic child before AED withdrawal following our routine epilepsy protocol).

An informed written consent was taken from care givers of patients subjected to the three month tapering. All of them were informed about the different opinions in this issue and other centers worldwide that practice this protocol. In fact, our study is not a trial of a new method of withdrawal of AEDs as multiple centers of Pediatric Neurology all over the world already practicing the three months withdrawal technique in their epilepsy protocols<sup>8,12</sup>. Some centers even performing routine withdrawal of treatment over only 4-6 weeks<sup>7</sup>.

All care givers had open access to hospital emergency department and informed with telephone numbers of Pediatric & Neurology staff to contact in any emergency.

**Statistical Analysis:**

All clinical and technical data were collected using the (Data Collection Form) and entered into a computerized database. Data obtained from all patients were statistically analyzed. Continuous variable were compared using analysis of variance for repeated measures. P-value < 0.05 was considered statistically significant. All data were expressed as mean ± standard deviation (mean± SD) or number (%) as appropriate. Data management was done by using SPSS version 14.

## RESULTS

The studied subjects (n=106) were categorized into two groups according to the duration of antiepileptic drug (AED) withdrawal after remission:

- \* Group I (n=61): Epileptic children with AED tapering over 6 months. This group was further divided according to the presence of relapse in one year follow-up into:
  - Group Ia (n=38) → children free from seizures on follow up.
  - Group Ib (n=23) → children with relapsed seizures on follow up.
- \* Group II (n=45): Epileptic children with AED tapering over 3 months or less. This group was further divided according to the presence of relapse in one year follow-up into:
  - Group IIa (n=27) → children free from seizures on follow-up.
  - Group IIb (n=18) → children with relapsed seizures on follow-up.

**Table 1.** Characteristics of the studied children with epilepsy (n=106).

Age (years):		
Mean±SD		8.8±2.4
Range		4-13
Gender:		
Male		61 (57.5 %)
Female		45 (42.5 %)
Positive family history of epilepsy:		24 (22.6 %)
Seizure free duration (months):		
Mean±SD		28.8±5.8
Range		24-48
Overall rate of relapse:		41/106 (38.7 %)
Abnormal EEG at the beginning of withdrawal:		32 (30.2 %)
Type of seizures:		
Partial		33 (31.1 %)
Generalized		73 (68.9 %)
Patients on two antiepileptic drugs		30 (28.3 %)

SD standard deviation

**Table 2.** Relapse of seizures regarding different duration of antiepileptic drugs withdrawal in children with epilepsy.

	Group (I) (≥ 6 months) (n = 61)		Group (II) (≤ 3 months) (n = 45)		X <sup>2</sup>	P
	N	%	N	%		
Free (a)	38	62.3	27	60	0.06	0.81 NS
Relapse (b)	23	37.7	18	40		

NS non-significant

**Table 3.** Relation between different parameters associated with relapsing of seizures in different groups of children with epilepsy.

	Group I b (≥ 6 months) (n = 23)		Group II b (≤ 3 months) (n = 18)		X <sup>2</sup>	P
	No	%	No	%		
Gender:						
Male	13	56.5	10	55.5	0.001	0.95 NS
Female	10	43.5	8	45.5		
Positive family history of epilepsy:	8	34.8	5	27.8	0.23	0.63 NS
Abnormal EEG:	5	21.7	12	66.7	8.4	0.003*
Type of seizures:						
Partial	9	39.1	8	44.45	0.12	0.73 NS
Generalized	14	60.9	10	55.55		
Number of drugs used:						
Two drug	8	34.8	7	38.9	0.07	0.78 NS
One drug	15	65.2	11	61.1		
Seizure free duration (months):					T	P
X̄±SD		28.2±4.2		29.1±6.4	0.51	0.59 NS
Range		24-36		24-46		

\*significant at p&lt;0.01   NS non-significant

**Table 4.** Relation between antiepileptic drugs used and relapse of seizures in different groups of children with epilepsy.

	Group I b ( $\geq 6$ months) (n =23)		Group II b ( $\leq 3$ months) (n =18)		X <sup>2</sup>	P
	No	%	No	%		
Valproic acid	8	34.8	6	33.3	0.01	0.92 NS
Carbamazepine	3	13	3	16.7	0.01	0.90 NS
Clonazepam	3	13	1	5.6	0.07	0.78 NS
Other drugs	1	4.4	1	5.6	0.31	0.58 NS
Two drugs	8	34.8	7	38.9	0.07	0.78 NS

NS non-significant

## DISCUSSION

Long term seizure control is the primary goal in the treatment of epilepsy and as a rule, once the patient is seizure free for at least 2 years antiepileptic drugs can be slowly discontinued<sup>13</sup>. No evidence based data is present to determine which rate of AEDs withdrawal is the best after control of epilepsy, so, further studies in this issue was recommended by many authors<sup>(14)</sup>; For this reason our study was performed on 106 epileptic children in remission to clarify this dilemma. Despite that a lot of restrictions and exclusion criteria were present, our study population was still homogenous and their characteristics are comparable to epilepsy findings in any community (Table 1); For example: Male gender were slightly higher than female (57.5% versus 42.5%) which is consistent with most recent studies that stated that gender-specific incidence in children is higher in males, although seldom significantly so<sup>15</sup>. Family history of epilepsy was present in 22.6% of patients which is expected<sup>15</sup>. The overall relapse rate (38.7%) despite being high but still consistent with multiple studies that recorded a relapse rate between 12 to 66%.<sup>4,9,12,16</sup> However, the relapse rate varies greatly according to the follow-up duration of different studies (between 6 months and up to ten years). Generalized epilepsy was the commonest type in the studied population (68.9%) (Table 1), which is the type reported to be common in developing countries without causal explanation<sup>15</sup>.

The relapse of seizure during one year follow up was not changed by the rate of AEDs withdrawal either over three or six months (Table 2). This finding is consistent with Tennison et al.<sup>17</sup>, who studied the relapse rate of seizures on 149 epileptic children and found no significant difference between six week and nine month tapering of AEDs on 39 months follow up<sup>17</sup>. Another more recent study performed on 57 children showed the same finding on comparing one month and six months withdrawal period after one year follow up<sup>6</sup>. Other studies reported the non-significant risk of relapsing

seizures whatever the duration of tapering of AEDs were also present<sup>7,12,14</sup>.

On the other side, an old study by Todt (1984) reported more risk of epilepsy relapse in rapid withdrawal of treatment<sup>18</sup>. The discrepancy between Todt's findings and ours may be attributed to the selection of severe epileptic patients on multiple medications in Todt's study; So, these results could not be a generalized finding for all children with epilepsy. Despite that the studies suggesting the favor of prolonged AEDs withdrawal are lacking, many physicians choose to withdraw AEDs slowly, based on the concept that if relapse occurs during the taper period, the seizure may be less severe than after full withdrawal<sup>12</sup>. This concept, however, has no scientific base and not supported by the results of our study. Factors that may influence the relapse of seizures during withdrawal of antiepileptic drugs were discussed in Table (3); We found that gender, presence of positive family history of epilepsy, type of seizures, seizure free duration and being on single or two AEDs have no effect on the relapse rate during withdrawal of treatment irrespective to the tapering duration i.e. AEDs can be withdrawn rapidly without respect of any variability in the previous parameters. The same findings were reported by Guerra et al. (2005) while comparing one month and six months tapering of AEDs in 57 epileptic children in remission<sup>6</sup>.

Abnormal EEG before AEDs withdrawal was significantly associated with seizure relapse if three months (rapid) withdrawal technique was performed (Table 3). This finding is different from Guerra et al. study<sup>6</sup>; However, fewer number of cases in Guerra, et al. study (57 case versus 106 in ours) may be the cause of this difference. The benefit of slowly withdrawing treatment in patients who still having abnormal EEG after remission may be related to the fact that abnormal EEG itself is usually associated with higher rate of recurrence of epilepsy<sup>12,16,19,20,21</sup>. So, we suppose that if our follow up duration was extended beyond one year, relapse would occur in other patients in group I which might eliminate the difference between both groups on long term follow up.

The number and nature of drugs used to achieve remission was not significantly associated with any increase in the risk of relapse of seizure either the rate of drug withdrawal was rapid or slow (Table 4); This finding, however, is limited by two factors:

- 1- Dividing the cases according to the drug used leads to the presence of few number of cases in each group that may affect the confidence of statistical data obtained.
- 2- Some drugs claimed to need prolonged tapering during withdrawal e.g. phenobarbitone & Phenytoin<sup>8,21</sup> were not included in our study because, they are rarely used in long term therapy in our epilepsy protocols.

### Conclusions

Withdrawal of antiepileptic drugs in children with epilepsy who achieve remission can be performed either rapidly (over three months) or slowly (over six months) without increasing the risk of seizure relapse. Cases with abnormal EEG before withdrawal are exception. In those cases slow withdrawal of treatment is recommended as rapid tapering might increase the risk of seizure relapse. So, we recommend that EEG must be done to patients before stopping AEDs so that rate of withdrawal should be slow in cases with abnormal EEG.

Regarding withdrawal of specific antiepileptic drugs used in therapy a large multicenter study is needed to evaluate the exact duration of withdrawal of each drug that carries the lowest risk of seizure relapse.

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### الملخص العربي

#### تأثير زمن سحب أدوية علاج الصرع على خطر تكرار التشنجات في الأطفال المصابين بالصرع

لا يوجد إجماع على الفترة الزمنية اللازمة لسحب الأدوية المضادة للصرع عند الأطفال المصابين بالصرع بعد خمود المرض لمدة سنتين. بعض المراكز المتخصصة تنصح بسرعة سحب الأدوية والبعض الآخر ينصح ببطئ السحب. ولقد صممت هذه الدراسة لمعرفة التأثير الفعال للسحب المبكر (ثلاثة اشهر) والسحب البطئ (ستة اشهر) للأدوية بالنسبة لتكرار التشنجات بعد سحب أدوية الصرع وكذلك دراسة المتغيرات المسؤولة عن عودة التشنجات في حالة السحب السريع والسحب البطئ. ولقد أجريت الدراسة الحالية على مائة وستة طفلاً بعد خمود النوبات الصرعية عنهم لمدة عامين على الأقل وتمت متابعة جميع الأطفال لفترة عام كامل لمتابعة حدوث أية نوبات. وقد تم تقسيم الأطفال إلى مجموعتين: شملت الأولى واحد وستون طفلاً تم إنقاص أدوية الصرع خلال فترة ستة شهور وشملت الثانية خمسة وأربعون طفلاً تم إنقاص الأدوية لهم خلال فترة ثلاثة شهور. وقد أثبتت الدراسة أن تكرار التشنجات بعد سحب أدوية الصرع لا يرتبط بالفترة الزمنية لإنقاص الأدوية سواء بالنسبة لنوع المريض (ذكر أم أنثى)، أو نوع الصرع، أو مدة عدم حدوث النوبات، أو عدد الأدوية المستخدمة للصرع، أو نوع الأدوية باستثناء الأطفال الذين كان رسم المخ الخاص بهم قبل إنقاص الأدوية غير طبيعي ولذلك يفضل سحب الأدوية الخاصة بالصرع في هؤلاء الأطفال (أصحاب رسم المخ الغير طبيعي) خلال ستة شهور على الأقل.