Impact of Drug Manipulation on Seizure Freedom in Adults with Uncontrolled Epilepsy: A Prospective Controlled Study in Rural China

*Xiaoting Hao MD, *Ziyi Chen MD PhD, Bo Yan MD, Patrick Kwan MD PhD, Dong Zhou MD PhD

Xiaoting Hao, Bo Yan, Dong Zhou: Department of Neurology, West China Hospital, Sichuan University, Chengdu, China

Ziyi Chen: Department of Neurology, The first Affiliated Hospital Sun Yat-sen University, Guangzhou

Patrick Kwan: 1. Departments of Medicine and Neurology, The University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, Australia; 2. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China

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Prof. Dong Zhou and Prof. Patrick Kwan are co-corresponding authors
1. Dong Zhou
   Department of Neurology, West China Hospital, Chengdu, Sichuan 610000, China
   Tel: +86 028 85422891
   Fax: +86 028 85422891
   Email: zhoudong66@yahoo.de
2. Patrick Kwan
   Department of Neurology, Royal Melbourne Hospital, Parkville, Australia
   Phone: +61 3 9342 7722
   Fax: +61 3 9342 8628
   Email: patrick.kwan@unimelb.edu.au

Xiaoting Hao hxt120@hotmail.com
Ziyi Chen chenziyi@mail.sysu.edu.cn
Bo Yan yanbo96@163.com
Patrick Kwan patrick.kwan@unimelb.edu.au
Dong Zhou zhoudong66@yahoo.de

* These authors contributed equally to the manuscript

Author Contributions

Xiaoting Hao: study concept and design, acquisition of data, statistical analysis, drafting of the manuscript.
Ziyi Chen: drafting of the manuscript, analysis and interpretation of data.
Bo Yan: acquisition of data.
Patrick Kwan: study concept, interpretation of data, critical revision of manuscript for intellectual content.
Dong Zhou: study supervision, study concept and design, interpretation of data, critical revision of manuscript for intellectual content.

Compliance with Ethical Standards

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Conflicts of interest

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Drs Xiaoting Hao, Ziyi Chen, Bo Yan, and Dong Zhou have no relevant conflicts of interest.

Ethical approval

The study was approved by the Institutional Ethics Committee of West China Hospital. All participants or their legal guardians provided written informed consent. The study was performed in accordance with ethics standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Abstract

Introduction

It has been suggested that uncontrolled epilepsy might not necessarily equate to drug resistance when antiepileptic drugs (AEDs) are used at relatively low doses, a practice frequently observed in rural areas of China.

Objective

To assess the clinical benefits of further drug manipulation in this situation, we prospectively followed up the outcomes of patients with uncontrolled epilepsy while taking relatively low doses of AEDs.

Methods

The study included patients aged 16 years and older with uncontrolled epilepsy and receiving at least one antiepileptic drug (AED) at dosage below 50% of the WHO defined daily dose (DDD) (Group 1). Patients with drug-resistant epilepsy were included for comparison (Group 2). Both groups were followed up for at least 2 years. Seizure outcomes after further drug manipulations were recorded at the last follow-up.

Results

A total of 197 patients (55.3% male) were included in Group 1 and 32 (46.9% male) in Group 2. Their mean duration of follow-up was 28.85±1.90 months and 30.91±2.04 months, respectively. At the last follow up, 16.8% (33/197) of patients in Group 1 had become seizure-free compared with none in Group 2 ($p<0.001$). Seventeen of 93 (18.3%) patients in Group 1 became seizure-free after increasing the dosage of baseline AED(s) alone. Only 5.5% (3/55) of patients who had failed to respond to an AED at ≥50% DDD at baseline became seizure-free, compared to 21.1% (30/142) who did not have such history ($p=0.001$). The number of AEDs taken at dosage below 50% DDD at baseline was not associated with seizure outcome.

Conclusions

Uncontrolled epilepsy could become controlled in a substantial proportion of patients by dose increase alone, particularly if there is no history of drug failure at ≥50% DDD.

Key Points

1. A substantial proportion of patients with uncontrolled epilepsy while taking AED treatment at relatively low doses could become seizure-free after further drug manipulations.
2. Dose increase alone could bring seizure freedom in some patients.
3. Patients with a history of drug failure at ≥50% DDD had lower chance to become seizure-free with further drug manipulations.

1 Introduction

Epilepsy affects 50 million people in the world, of whom 80% live in low- to middle-income countries[1]. In rural areas of China, approximately 40% of patients have never received appropriate antiepileptic drug (AED) therapy, and two thirds of patients with active epilepsy are untreated[1]. Even with treatment, epilepsy is uncontrolled in more than 70% of patients in rural China[2]. Uncontrolled epilepsy is associated with increased mortality and morbidity[3]. It may also restrict the patient's social activities, placing stress on the family members, as well as substantial economic burden for the society, both in direct healthcare costs and loss of productivity[4].

Through applying the definition of drug-resistant epilepsy promoted by the International League Against Epilepsy (ILAE), our previous study suggested that "uncontrolled" epilepsy might not necessarily equate to drug-resistance[5]. This could have arisen because the AEDs are used at relatively low doses[5], a practice commonly observed in rural areas of China[1]. In this situation, there is often an impression that multiple AEDs have "failed" to control the epilepsy, leading to a sense of pessimism on the likely success of further drug changes.

To assess the clinical benefits of further drug manipulation in this situation, we prospectively followed up the outcomes of patients with uncontrolled epilepsy while taking relatively low doses of AEDs. We hypothesized that a substantial proportion of such patients could become seizure-free with further AED manipulations.

2 Methods

2.1 Design and setting

This was a prospective observational cohort study. Consecutive patients attending the epilepsy clinic of West China Hospital for the first time between Dec 3, 2010 and Aug 18, 2011 were enrolled and followed up until Jan 28, 2014. The study was approved by the Institutional Ethics Committee of West China Hospital. All participants or their legal guardians provided written informed consent.

Patients were referred from primary care clinics in Sichuan province, mostly situated in the rural areas[2,6]. Patients were screened for eligibility of inclusion if they had been diagnosed with epilepsy for at least 1 year, and were 16 years of age or older. Patients who were being evaluated for epilepsy surgery, or those with uncontrolled psychiatric disorders, progressive intracranial pathologies, or severe renal or hepatic impairment were excluded. Patients who were not receiving AED therapy were also excluded.

2.2 Definitions and patient groups

Drug responsiveness was categorized according to the ILAE definition[7]. Seizure freedom was defined as no seizure for at least 12 months or three times the pre-treatment inter-seizure interval, whichever was longer. Patients who were not seizure-free while taking at least one AED were considered to have "uncontrolled" epilepsy. Among these patients, they were regarded as having drug-resistant epilepsy if they had been treated with two or more AEDs appropriately. The term "appropriate" required the AED to be appropriate for the patient's epilepsy and seizure type, and taken at adequate dosage for a sufficient length of time. The ILAE definition did not stipulate specific criteria for adequate (or high vs. low) dosage. Therefore, similar to our previous study[5], "low" dosage in this study was defined as less than 50% of the defined daily dose (DDD) according to the World Health Organization (WHO)[8], taken for least 3 months. This definition has been shown to have predictive value on subsequent drug response[9].

In patients with uncontrolled epilepsy who did not fulfill the definition of being drug-resistant, the drug responsiveness was classified as "undefined", and the reasons were recorded.

Two groups of patients were included in this study. Patients with undefined drug responsiveness and receiving at least one AED at low dose (<50% DDD) at baseline, and had at least 1 seizure during the previous 6 months were recruited into Group 1. Patients who fulfilled the definition of having drug-resistant epilepsy were followed up for comparison (Group 2).

2.3 Study procedures

Demographic and clinical information was collected at baseline. Drug responsiveness was evaluated according to ILAE definition as described above[7]. Manipulation strategy (i.e. dosage increase or substitution with/addition of a different drug) for the AED(s) that the patient was receiving at dose(s) < 50% DDD, was decided at the discretion of the treating neurologist in consultation with the patient, taking into account seizure frequency and adverse effects and, in some occasions, economic factors. Patients in both groups were followed up at the clinic at least every 3 months for at least 2 years. At the last follow-up, responsiveness to AED treatment was evaluated again.

2.4 Statistical analysis

Patients in Group 1 were divided into three distinct subgroups based on the drug manipulation strategies adopted. In subgroup 1, only the dosage of baseline AED(s) was increased (to ≥50% DDD); in subgroup 2, AED(s) was replaced or additional AED(s) was prescribed without increase of baseline AED dosage; in subgroup 3, there was both prescription of additional AED(s) and dosage increase of baseline AED(s) (irrespective of whether dosage was increased to ≥50% DDD). The Chi-square test and Fisher's exact test were used as appropriate to compare categorical variables between patients who were seizures-free and those with drug-resistant epilepsy at the last follow-up. Analysis of variance (ANOVA) was used to compare group means. Kaplan-Meier analysis was performed for time to seizure freedom both on the whole Group and the subgroups of different drug manipulation strategies. Analyses were conducted with SPSS 17.0 (SPSS Inc., Chicago, IL). P<0.05 was considered as statistically significant.

3 Results

3.1 Baseline characteristics

A total of 397 patients were screened during the study period (Figure 1). At baseline, 55 patients were seizure-free while 342 had uncontrolled epilepsy. In the latter group, 37 fulfilled the definition of having drug-resistant epilepsy, while the remaining 305 had undefined drug responsiveness. The study population consisted of 197 patients in Group 1 who had undefined drug responsiveness and were taking at least one AED at low dosage (<50% DDD), of whom 133 (67.5%) were taking two or more AEDs, and 32 patients who had drug resistant epilepsy (Group 2) at baseline. Table 1 shows the characteristics of these two groups. There was no significant difference in age, and gender at baseline between two groups. Not surprisingly, patients with drug-resistant epilepsy were taking a higher number of AEDs and had longer duration of epilepsy.

3.2 Overall seizure outcomes

The mean duration of follow-up was 28.85±1.90 months in Group 1 and 30.91±2.04 months in Group 2. At the last follow-up visit, 33 (16.8%) of the 197 patients in Group 1 had become seizure-free, compared with none in Group 2 (p<0.001). Kaplan-Meier analysis (Figure 2) confirmed that Group 1 had a higher chance of becoming seizure-free compared with Group 2 (p=0.006). At the end of follow-up, 54 (27.4%) patients in Group 1 became drug-resistant and 110 (55.8%) still had undefined drug responsiveness, of whom 48 were taking AED(s) at doses <50% DDD because they were reluctant for dose increase.

3.3 Seizure outcomes with different drug manipulation strategies

Among Group 1, 93 patients had only dose increase of existing AED(s) to ≥50% DDD (subgroup 1), 36 were prescribed new AED(s) only (subgroup 2), and 68 received additional AED(s) after dosage increase (subgroup 3). In subgroup 1, 18.3% (17/93) of patients became seizure-free, while 30.6% (11/36) did so in subgroup 2. Both Chi-square and Kaplan-Meier analysis showed that the probability of seizure freedom between these two strategies did not differ significantly (p=0.155 and p=0.07, respectively; Figure 3). In subgroup 3, four of 68 (5.9%) patients became seizure-free when additional AED(s) was prescribed, after dose increase alone did not achieve seizure freedom. They comprised of two of 39 patients in whom the dosage was increased to ≥50% DDD, and two of 29 patients in whom the dosage did not reach 50% DDD.

In Group 2 (n=32), additional AEDs were prescribed in 21 patients, 4 patients had increased dosage only, while 7 patients had new AEDs added after dose increase. None became seizure-free.

3.4 Predictors of seizure outcomes

Table 2 shows the baseline characteristics in patients with different seizure outcomes at last follow-up in Group 1. A larger proportion of patients who became seizure-free had only been exposed to one AED (51.5%) compared to those who became drug-resistant

(14.8%) or who remained to have undefined drug responsiveness (35.5%; p=0.01). Consistent with this, patients who did not have any previously discontinued AEDs, or were taking fewer baseline AEDs at the time of recruitment, were more likely to become seizure-free at the end of follow up (Table 2). There was no significant difference in sex, epilepsy syndrome, age of onset of epilepsy, age at recruitment, or duration of epilepsy or of treatment between patients with different outcomes.

Nearly half of the patients in Group 1 were taking more than one AED at low doses (94/197, 47.7%). The number of baseline AEDs taken at low dosages was not associated with seizure outcome (Table 3). However, only 5.5% (3/55) of patients who had a history of failing to respond to an AED at dosage ≥50% DDD became seizure-free, compared with 21.1% (30/142) who did not have such history (p=0.001).

4 Discussion

In this prospective study, we observed that within a mean follow up of 2.5 years, approximately 1 in 6 patients with seemingly uncontrolled epilepsy while taking AED treatment at relatively low doses were able to achieve seizure freedom after further drug manipulations. In contrast, none of the patients with drug-resistant epilepsy, having already failed to respond to adequate trials of two or more AEDs, became seizure-free, despite undergoing further drug changes. This observation supports the notion that "uncontrolled" epilepsy does not necessarily imply drug resistance if the AEDs have not been trialed adequately[5]. Previous studies have also shown that patients in whom two or more AEDs have failed could become seizure-free after further drug trials, although the doses taken were usually not reported[10-11]. In a recent long-term outcome study of patients fulfilling the definition of drug resistance, a substantial proportion achieved seizure freedom later, albeit with a delay of many years (median follow up was 40 years)[12]. Further, the study by Sillanpää and Schmidt included only childhood onset (0-16 years) epilepsy, the prognosis of which may be more favourable than epilepsy beginning in adulthood, as in our study where the mean onset age was 21.5 years[12].

Remarkably, increasing the dosage to ≥50% DDD alone seemed to be as effective as switching to or adding new medications in rendering patients seizure-free. This is consistent with a previous report by Schmidt in 1983, which showed a similar benefit of increasing drug doses.[13] This observation also concurs with our previous findings that in patients with persistent seizures while taking low dose oxcarbazepine, there was no difference in subsequent seizure control between dose increase and addition of another AED[14]. It has previously been shown in patients with newly diagnosed epilepsy that failure of the first AED at higher doses predicted poorer response to subsequent AEDs[9], and 50% of the DDD has been proposed to be an appropriate cutoff to define an adequate trial. By applying this cutoff prospectively, findings from this study lend further support to its use in defining adequacy of drug trial, hence it may be used to guide management strategies.

Patients with persistent seizures while taking at least one AED at dosage of ≥50% DDD were significantly less likely to become seizure free upon further drug manipulations compared to those whose AEDs were all at low doses. Among the former group, <6% became seizure free, compared with >20% in the others (Table 3). Persistent seizures while taking adequate doses suggest failure due to lack of efficacy. This observation is in line with previous findings that failure of the first AED due to lack of efficacy is a strong predictor of poor outcome, compared with failure due to other reasons. Among these patients, only 11% became seizure-free in the long-term[15].

It is encouraging to observe that outcome was not associated with the number of AEDs taken at low doses at baseline. This further supports the general recommendation to ensure adequate dosage of monotherapy before addition of other AEDs[17]. Usage of monotherapy has the advantages of minimizing the risk of toxicity, prevention of drug interactions, and facilitating the assessment of drug response[18].

Treatment gap is generally defined as the proportion of patients with active epilepsy who are not receiving AED therapy[1]. We propose that because of the suboptimal response, usage of inadequate doses of AEDs also represents a form of treatment gap. Our study showed that many patients are being treated with multiple AEDs at inadequate doses in rural China. Economic factors may have limited the use of higher doses in rural West China, where annual household income is <USD4,500 for 90% of patients[2]. We speculate that this prescribing behavior may also reflect entrenched beliefs of both clinicians and patients with roots in traditional Chinese medicine practice, which tends to use multiple medicinal herbs at small doses. Professional societies and patient support groups can play a major role in educating both the clinicians and patients on the optimal use of AED therapy[2,19-20]. Establishing a network model linking rural clinics with provincial specialist centers may improve adherence to treatment guidelines[21].

This study is limited by the small sample size and non-randomized design. Only adults recruited from specialist clinics were included, hence the findings may not be generalizable to children and the primary care setting. In clinical practice, multiple internal and external factors should be considered in dose adjustment, such as the age of patients, any interaction with concomitant medications, and the patient's hepatic and renal functions. An individualized approach is needed. Nonetheless, these data show that seemingly uncontrolled epilepsy can become controlled in a substantial proportion of patients. In these patients the reasons for persistent seizures should be carefully explored. Before switching to or adding a new medication, dose increase should be considered if relatively low dosages (<50% DDD) are being used which may lead to favorable outcome, particularly if the patient has never failed an AED at adequate dosage. This approach may help avoid the use of polypharmacy, which increases the risk of drug interactions, adverse effects and even seizure aggravation.[13,16,18]

5 Conclusions

A substantial proportion of patients with uncontrolled epilepsy while taking AED treatment at relatively low doses could become seizure-free after further drug manipulations. This could be achieved by dose increase alone in some patients, particularly if all the AEDs failed were taken at low doses.

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Table 1. Baseline characteristics of patient groups.

	Group 1 (n=197)	**Group 2 (n=32)**	**P value**
Male, n (%)	109 (55.3%)	15 (46.9%)	0.45[a]
Age at recruitment (years), mean ±SD	29.4 ±12.7	31.0±11.6	0.51[b]
Age of onset of epilepsy (years), mean ±SD	21.5±9.8	17.5±11.0	0.102[b]
Duration of epilepsy (years), mean ±SD	6.3±5.3	13.6±8.6	<0.001[b]
Structural/metabolic epilepsy	57 (28.9%)	12 (37.5%)	0.41[a]

Number of antiepileptic drugs, median (range)	2 (1-5)	3 (2-5)	<0.001[c]

a, by Student's t-test; b, by Chi-square test; c, by Mann-Whitney U test

Table 2. Relationship between baseline characteristics and seizure outcome at the last follow-up in Group 1.

Baseline characteristics	Seizure-free (n=33)	Drug-resistant (n=54)	Undefined (n=110)	P value	Total (n=197)
Male	17 (51.5%)	28 (51.9%)	64 (58.2%)	0.67[a]	109 (55.3%)
Age at recruitment (years), mean ±SD	26.2±9.8	29.7±12.1	30.2±13.6	0.28[b]	29.4±12.7
Age of onset of epilepsy (years), mean ±SD	20.2±5.5	20.7±4.9	22.2±12.3	0.484[b]	21.5±9.8
Duration of epilepsy (years), mean ±SD	6.3±5.3	8.9±7.8	7.8±9.2	0.35[b]	7.9±8.3
Duration of treatment (years), mean ±SD	4.4±3.5	6.7±7.3	5.1±8.6	0.34[b]	5.4±7.1
Total no. of AEDs exposed					
1	17 (51.5%)	8 (14.8%)	39 (35.5%)		64 (32.5%)
2	12 (36.4%)	27 (50.0%)	43 (39.1%)		82 (41.6%)
3	3 (9.1%)	12 (22.2%)	22 (20.0%)	0.01[a]	37 (18.8%)
≥4	1 (3.1%)	7 (13.0%)	6 (5.5%)		14 (7.1%)
No. of previous (discontinued) AEDs					
0	31 (93.6%)	38 (70.4%)	89(80.9%)		158(80.2%)
≥1	2 (6.1%)	16 (29.6%)	21(19.1%)	0.027[a]	39(19.8%)
No. of baseline AEDs at recruitment					
1	20 (60.6%)	11(20.4%)	44 (40.0%)	0.004[a]	75(38.1%)

2	11 (33.3%)	32(59.3%)	53 (48.2%)	96(48.7%)
≥3	2 (6.0%)	11 (20.4%)	13 (11.8%)	26(13.2%)

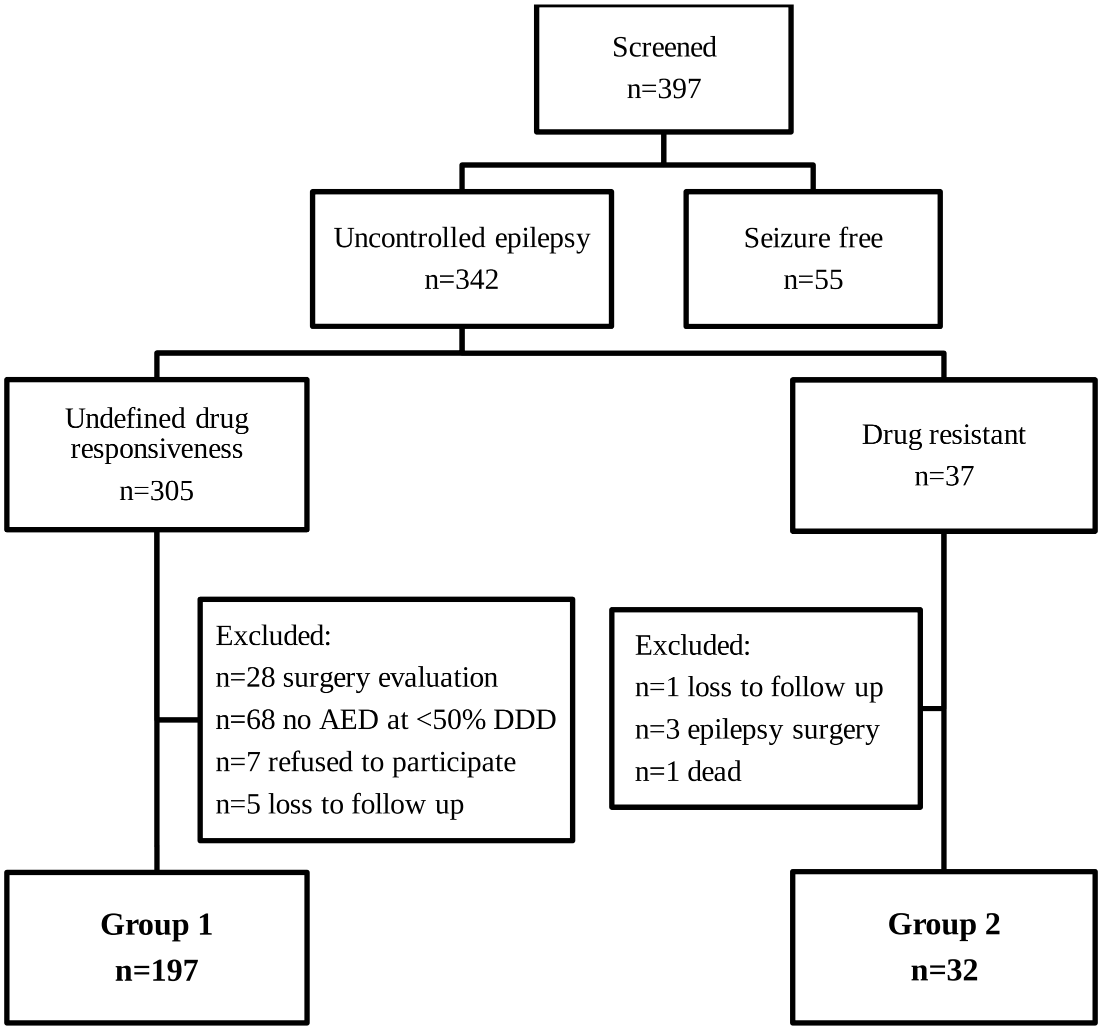
a, by Chi-square test; b, by analysis of variance; AEDs, antiepileptic drugs

Table 3. Relationship between dosage of baseline antiepileptic drugs and seizure outcome at the last follow-up in Group 1.

	Seizure-free (n=33)	Not seizure-free (n=164)	P value	Total (n=197)
Number of AEDs with dose <50% DDD, n (% of group)				
1	19 (18.4%)	84 (81.6%)	0.71	103
2	11 (16.4%)	56 (83.6%)		67
3	3 (13.6%)	19 (86.4%)		22
4	0 (0%)	5 (100%)		5
Failure of 1 AED with dose ≥50% DDD, n (% of group)				
Yes	3 (5.5%)	52 (94.5%)	0.001	55
No	30 (21.1%)	112 (78.9%)		142

AEDs, antiepileptic drugs; DDD, defined daily dose

Figure 1. Patients flow



1. AED: antiepileptic drug; 2. DDD: defined daily dose

Figure 2. Kaplan-Meier analysis for time to seizure freedom. Outcome comparison of Group 1 and Group 2 showed significant differences ($P_{log\ rank}$=0.006). Data were censored when the patient reached the last follow-up and completed study.

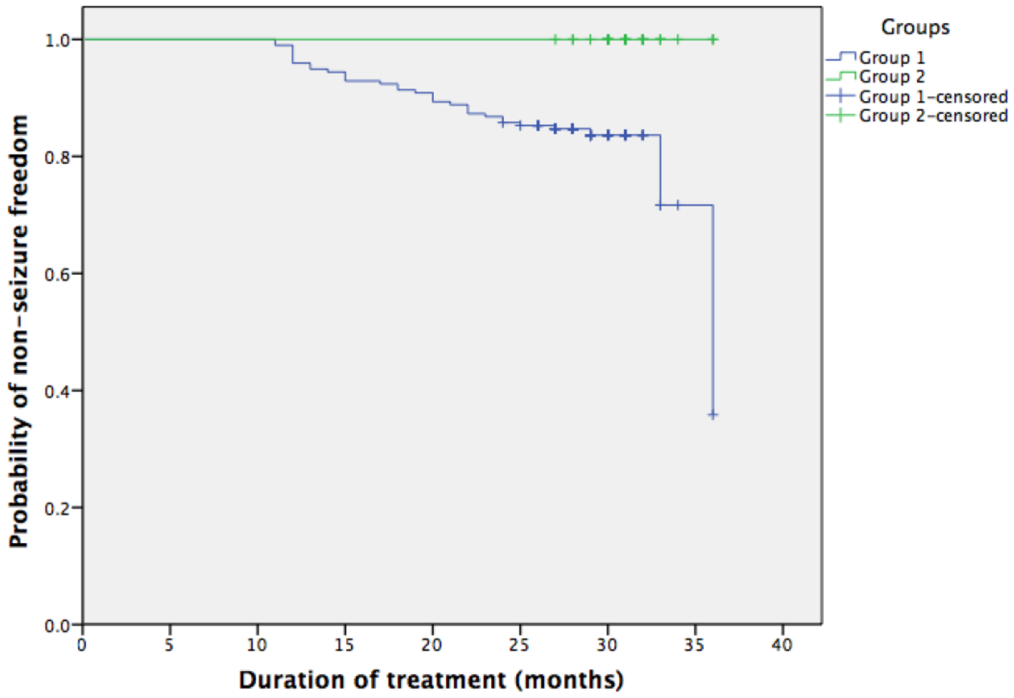
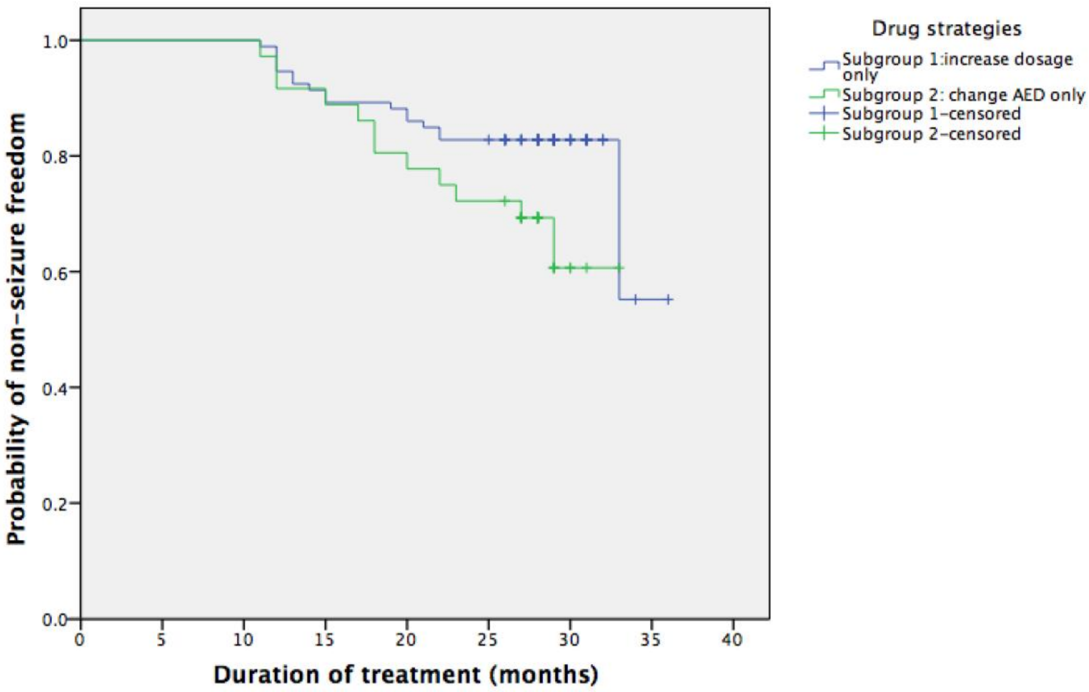


Figure 3. Kaplan-Meier curve for seizure freedom in patients treated with different drug manipulation strategies. $P_{log\ rank}$=0.070. Data were censored when the patient reached the last follow-up and completed study.



Probability of non-seizure freedom
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
35
40
Duration of treatment (months)
Drug strategies
Subgroup 1:increase dosage only
Subgroup 2: change AED only
Subgroup 1-censored
Subgroup 2-censored