Monotherapy or Combined therapy in non-responding Epilepsy, Which is best?

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Abstract

Background: Epilepsy is one of the most prevalent chronic diseases (4/1000 children and 7/1000 adult worldwide). It is also associated with significant increased risk of psychiatric disorder and family distress. Treatment consists of anticonvulsants medications, lifestyle modification and psycho education. The compliance of the patient with treatment is very important for the management of epilepsy however, the subject has not been widely investigated.

Subjects and methods: A convenient cross-sectional study was conducted among 113 patients (62 females and 51 males) with uncontrolled epileptic in a tertiary care center in AL Hussieny Teaching hospital in Kerbala and the Medical City in Baghdad / Iraq and the later represents the main center dealing with non-responding patients referred from all over the country. A special survey questionnaire form was prepared for this purpose including demographic information in addition to family history, type of epilepsy and treatment. In addition the results of investigations performed were assessed including: Video Electro-Encephalogram (EEG,) and Magnetic Resonance Imaging (MRI).

Results: The mean age of the sample was 25.27±15.14 year and no significant gender difference was discovered. The monotherapy group of patients were younger than combined therapy group however the difference in age was not significant (p=.275). Most patients (71%, 80 patients) were in the monotherapy group, while only 29% (33 patients) were in the Combined therapy group. Video EEG was abnormal in 69.9% of (79 patients) of the total sample, while it was positive in 36% in combined therapy patients vs. 27% in monotherapy patients. Similarly, MRI was abnormality was encountered more in the combined therapy group (21% vs.14%). The main finding for this study was that monptherapy type of treatment was better in controlling epilepsy with highly significant difference (61% vs. 28%, p<.001). Additionally, the significant predictors of epileptic fit were positive family history and duration of disease.

Conclusions: Monotherapy was found to be significantly better than combined therapy in controlling fit among patients with uncontrolled epileptic in tertiary care centers in Iraq.

Keywords:
Epilepsy, monotherapy, combined therapy, tertiary care center
Conflict of interest: None

Introduction

Epilepsy is defined as a condition of recurrent, unprovoked seizure (1). A "seizure is a paroxysmal alteration of neurologic function caused by the excessive, hyper synchronous discharge of neurons in the brain'' (2).

The lifetime prevalence of epilepsy is around 7.60 per 1,000 persons (3), which makes the disease among the most common neurological diseases. Epilepsy has numerous causes, each reflecting a type of underlying brain dysfunction (2). Familial incidence of epilepsy is well recognized as with generalized epilepsy there is eightfold higher risk compared to general population (4).

About 65 million people worldwide have epilepsy (5), and this makes it one of the most common global neurological disease. About 80% of the people with epilepsy live in low-and middle-income countries. A complicating problem in these countries, epileptic patients and their families suffer from stigma and discrimination (6).

A specialist team from WHO concluded that epilepsy is responsible for 0.5% of the expenditure allotted for worldwide incapacitating diseases and proposed actions that would reduce the incapability of patients with epilepsy (7).

The global burden of epilepsy is extending as the DALY increased by 30% between 1990 and 2010 (8). Epilepsy is not a public health problem alone, but represents a profound social problem to the family and the community as a whole. In developing countries, epilepsy diagnosis carries a markedly embarrassing social stigma. For this reason, the patient is affected by an emotional factor due to the lack of information about epilepsy in the community (7, 9). The patients are afraid of socially assuming their epileptic condition fearing social discrimination and stigmatization: they are unable to find employment. Genetic influence of epilepsy was documented through the follow up of first degree relatives of epileptics in a large cohort; the Rochester Epidemiology Project. There was an increase in the risk for focal epilepsy among relatives of both generalized (2.5-fold) or focal epilepsy (2.6-fold) (10).

Patients without treatment are unable to work and/or need constant family supervision. On the other hand, untreated patients with epilepsy require repeated hospitalization due to the occurrence of epileptic fits or the accidents and trauma caused by the epilepsy (11). People with epilepsy respond to treatment approximately 70% of the time 12)13 ,(.

Evidence based guidelines should form the base for the choice of antiepileptic drug for an epileptic patient based on the best quality regarding possible epileptic fits and harms of the specific treatments.

A single antiepileptic drug (AED) is the main line of treating epileptic patients and is estimated to be used in more than two third of them (14-20). Monotherapy usually results in remission in 60-70% of patients directly after treatment (12, 19).

Throughout the earlier years of the twentieth century, the standard AEDs (Phenytoin, Phenobarbital, Primidone, Valproic acid, Carbamazepine, and Ethosuximide) were given in combination due to the wide belief that combined therapy was more effective than monotherapy. A change occurred during the 1970s, as many studies suggested that monotherapy was equally efficacious, less toxic, and more tolerable than combined therapy. Thereafter, most neurologists have advocated monotherapy as the preferred approach in epilepsy, although combined therapy is indicated in some cases (16, 21).

About one third (20-30%) might remain to have drug resistant epilepsy with continuing seizures, increased mortality, adverse effects and substantial psychiatric and somatic comorbidities. Newer AEDs have increased treatment options and simplified the use; but do not reduce the frequency of drug resistant epilepsy or prevent epilepsy in those at risk (12, 15).

The selection of the type of AED in a newly diagnosed patient depends on the type of epilepsy, tolerability (lowest toxicity) and availability. Current guidelines recommend valproate (VPA) as a treatment of first choice for patients with generalized onset seizures whilst carbamazepine is recommended as the first line treatment for patients with partial onset seizures Epileptic seizures have been observed since antiquity (15, 22). The selected AED should be reduced or discontinued gradually, when a decision to start a second AED with different mechanism of action is taken. Refractory epilepsy cases are in need for combined therapy.

About one third of patients with epilepsy will not respond to monotherapy, and they become candidates for combined therapy. When optimum monotherapy fails, the value of combined therapy is not yet clear. In chronic patients on combined therapy there may be scope for careful rationalization to two or sometimes one drug, with reduction in chronic toxicity and sometimes improved seizure control.

A recent systematic review of studies among 1769 patients to assess five year seizure free proportion in those who stopped taking drug reported that relapse occurred in 812 (46%) of patients, 9% had seizures in their last year of follow-up suggesting enduring seizure control was not regained. Independent predictors of seizure recurrence were: epilepsy duration before remission, seizure-free interval before AED withdrawal, age at onset of epilepsy and abnormal EEG (23).

Furthermore, such studies can also examine whether the careful and effective treatment of seizures at their onset may ultimately improve the present unsatisfactory long-term prognosis. Finally, it should be apparent that there are advantages in this approach to drug therapy which extend beyond the pharmacological control of seizures. If seizures are treated in the simplest and most effective way with one or, at the most, two drug items (24).

For specific drug items, Lamotrigine is clinically superior to all other antiepileptic drugs in cases of treatment failure; however some studies suggest a disadvantage compared to carbamazepine for time to 12 month remission. A systematic review of 20 randomized trials including more than six thousand patients, concluded that for focal seizures, lamotrigine, carbamazepine and oxcarbazepine provide the best combination of seizure control and epilepsy treatment failure (25). A recent review concluded that current guidance (e.g. NICE) that the first-line treatment for partial onset seizures is carbamazepine and lamotrigine, in addition levetiracetam may be a suitable alternative (26).

A recent systematic review for articles between 1985 and 2014 includes 10 926 article about the guideline for treatment of epilepsy conclude identified substantial gaps in this disciplines (22), and a similar conclusion was made on surveying a group of 42 physicians across the United States (27).

In Iraq, a cross-sectional study among 200 patients in a northern city (Sulaymania) reported treating 75.5% of them with single drug and showed that patients' compliance was good (62%) which was not associated with the type of treatment (28). A second study explored the etiologies, diagnosis and treatment of adult onset epilepsy in Babylon

governorate in the middle part of Iraq. It revealed that EEG was positive in (57.3%) of cases and the MRI was conclusive in 63.7% of them in (29). A third recent study investigated the main causes of resistant epilepsy in a tertiary care hospital in Baghdad and concluded that in most cases (36%) the reason was poor compliance. Compliance was found to be statistically associated with abnormal EEG finding, past medical history (hypertension, cardiac diseases, encephalitis, diabetes mellitus and any significant history) and quality of follow up. The follow-up was found to be statistically associated with the family history, past medical history (encephalitis and hypertension) and compliance of patient.

Subjects and methods

This cross sectional retrospective study tried to compare monotherapy and poly therapies in patients with uncontrolled epileptic in two centers (the Medical City in Baghdad /Iraq and Al Hussieny hospital in Kerbala/Iraq in the period between 1st January 2018 and 31st October 2018. These centers are tertiary care centers dealing with non-responding epileptic patients referred from other health premises. A special survey form was prepared for this purpose including potential predictors related to epilepsy treatment (23), including: demographic information in addition to family history, type of epilepsy according to the International League against Epilepsy (ILAE) (30), and treatment history, response to treatment over six months and investigations done for each patient including: Video Electro-Encephalogram (EEG,) findings brain Magnetic Resonance Imaging (MRI) findings indicating organic lesion in the brain (31).

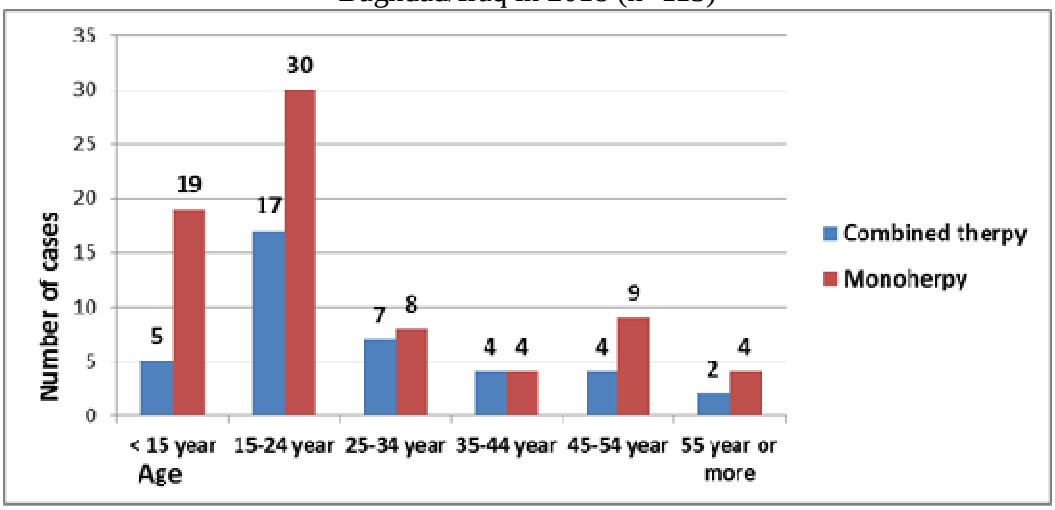
Results

A total of 113 epileptic patients were included in a convenient sample in this study with a mean age 25.27±15.14 year and a range extending between seven months and 68 year. One fifth of the patients (21 patients) aged below fifteen year (21.24%). The females formed the more than one half (54.9%, 62 patient), while males formed the remaining 45.1% (51 patient). Male patients were older than female patients in the sample, but no significant gender difference was found in mean age (the mean age of females was 23.89 ± 15.33 year, while male mean age was 26.54± 14.88, p=.158). The duration of disease extended between two months and 30 year and a mean of 7.34 ± 6.46 year. Drug compliance of epileptic patients was satisfactory as 59.3% of the patients reported taking medications regularly. Compliance was significantly associated duration of disease (p=.040) and age category (.030), while it was not associated all other predictors. Investigations among this sample showed that positive EEG findings were seen in 69.9%, while MRI findings were positive in only 15.9% of cases. Both investigations were significantly associated with the duration of disease.

Most patients (65.5%, 74 patient) were in the monotherapy group, while only 34.5% (39 patient) were in the combined therapy group. There was no significant gender difference between the two types of treatment (p=.381). The mean age of patients in the monotherapy group was a 24.29± 15. 71 year, while those in those the combined therapy group were older with a mean age of 27.13±13.99 year, however the difference was not significant (p=.346). The combined therapy group of patients included five patients aged below fifteen year (12.8%) while about one half (48.6%) of the patients in the monotherapy group were below 15 years of age (figure 1). Giving combined therapy does not decreased patient's compliance with treatment as judged by taking treatment regularly (p=.280).

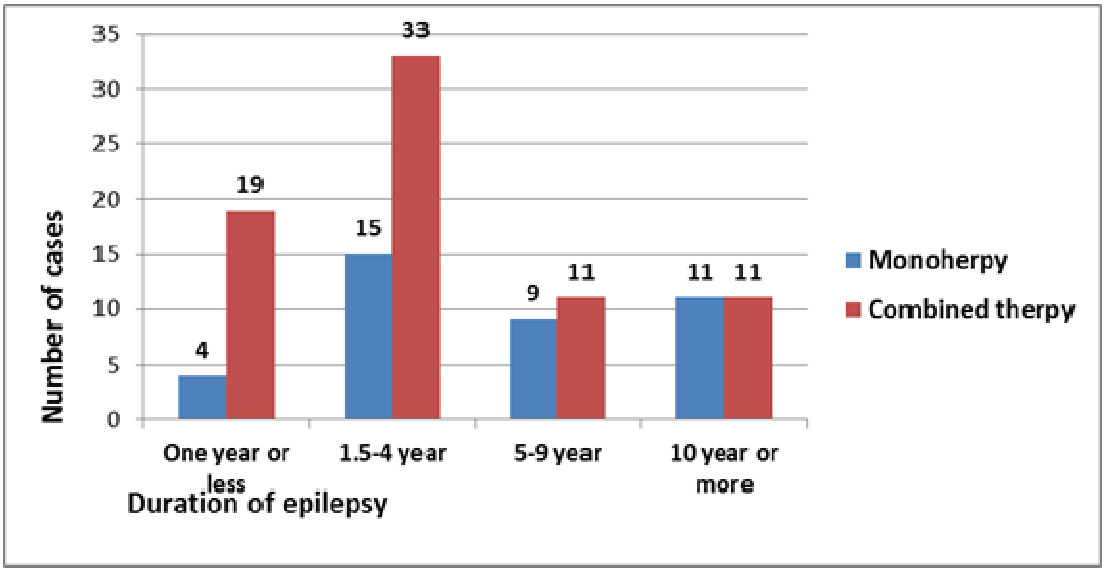
Figure 1: The age distribution of monotherapy and combined therapy groups of epileptic

patients in Al-Hussieny Teaching hospital in holy Kerbala and Medical city in Baghdad/Iraq in 2018 (n=113)



The monoherapy group of patients included 52 patients complained of epilepsy below five years (70.3%), while in the combined therapy group there was five patients with a duration of disease below five years (12.8%, figure 2).

Figure 2: The distribution of duration of disease of monotherapy and combined therapy groups of epileptic patients in Al-Hussieny Teaching hospital in holy Kerbala and Medical city in Baghdad/Iraq in 2018 (n=113)



Comparison of treatment results between monotherapy and combined therapy showed that the first was superior as epilepsy was controlled in 60.8% of those on monotherapy, while the disease was controlled in only 28.2% of those on combined therapy and the difference was highly significant. A significant difference was also discovered for positive family history of epilepsy which was positive in 12.2% of monotherapy group compared to more

than double the proportion (28.2%) of the combined therapy group. While, no significant difference was observed for all other variables (table 1).

Variable	**Groups**	**Monotherapy**		**Combination therapy**		**Total**		
		Freq.	**Percent.**	**Freq.**	**Percent.**	**Freq.**	**Percent.**	
Gender	Male	34	45.95	17	43.59	51	45.13	0.811
	Female	40	54.05	22	56.41	62	54.87	
Family history	Negative	65	87.84	28	71.79	20	17.70	**0.034**
	Positive	9	12.16	11	28.21	93	82.30	
Age category	< 15 year	19	25.68	5	12.82	24	21.24	0.57
	15-14 year	30	40.54	17	43.59	47	41.59	
	25-34 year	8	10.81	7	17.95	15	13.27	
	35-44 year	4	5.41	4	10.26	8	7.08	
	45-54 year	9	12.16	4	10.26	13	11.50	
	55 year or more	4	5.41	2	5.13	6	5.31	
Duration of disease	One year or less	19	25.68	4	10.26	23	20.35	0.089
	1.5-4 year	33	44.59	15	38.46	48	42.48	
	5-9 year	11	14.86	9	23.08	20	17.70	
	10 year or more	11	14.86	11	28.21	22	19.47	
Compliance with treatment	Irregular	31	41.89	15	38.46	46	40.71	0.724
	regular	43	58.11	24	61.54	67	59.29	
Smoking	Smoker	9	12.16	6	15.38	15	13.30	0.631
	Non-smoker	65	87.84	33	84.62	98	86.70	
Type of epileptic fit	Focal	18	24.32	10	0.33	30	26.55	
	General	56	75.68	29	0.67	83	73.45	
Video EEG	Abnormal	20	27.03	14	35.90	79	69.91	0.328
	Normal	54	72.97	25	64.10	34	30.09	
MRI	Abnormal	10	13.51	8	20.51	95	84.07	0.334
	Normal	64	86.49	31	79.49	18	15.93	
Control*	Negative	29	39.19	28	71.79	56	49.56	**<0.001**
	Positive	45	60.81	11	28.21	57	50.44	
Total		74	65.50	39	34.50	113	100.00	

* No epileptic fit for six months

Table 2: The distribution of demographic and clinical characteristics of disease of epileptic patients treated by monotherapy and combined therapy in in Al-Hussieny Teaching hospital in holy Kerbala and Medical city in Baghdad/Iraq in 2018 (n=113)

The type of epileptic fit was detrimental in the result of treatment of epilepsy, as the epileptic fit was controlled in 60.0% of the patients with focal epileptic fit compared to 45.8% of those with generalized epileptic fit and the odds ratio was 1.78 (table 2). In

addition, the duration of disease was different among the different types of epilepsy. Three quarters (73.3%) of those with focal epileptic fit suffered from the disease since less than five years compared to 59.1% among generalized epileptic fit patients, however the difference was not significant (p=.179). Investigation performed in the two types also showed some differences, as EEG findings were positive in 80% of those with focal epilepsy compare to two thirds (66%) of those with generalized epileptic fit, however the difference was not significant (p=.160). For MRI findings, positive results were discovered I 23% and 13% in those with focal and generalized epileptic fit, respectively.

Type of epileptic fit	**Indicator**	**Controlled epilepsy***		**Total**
		Negative	**Positive**	
Focal epileptic fit	Count	12	18	30
	Percentage	40.0%	60.0%	100.0%
Generalized epileptic fit	Count	45	38	83
	Percentage	54.2%	45.8%	100.0%
Total	Count	57	56	113
	Percentage	50.4%	49.6%	100.0%

* No epileptic fit for six months (p=.182)

Table 2: The distribution of control of epileptic fit in epilepsy by the type of epilepsy treated by monotherapy and combined therapy in in Al-Hussieny Teaching hospital Kerbala/Iraq and Medical city in Baghdad in 2018 (n=113)

Similarly, the duration of diseases was a significant determinant of epileptic fit control in epilepsy (table 3). When analysis was done with in each treatment type separately, the duration of disease was significant only in the monotherapy group (p= 033). The proportions of patients with controlled fit in monotherapy group were 68.4% and 72.7% for those who had the disease for one year or less and 1.5-4 year, respectively. These proportions were significantly higher than those who had the diseases for 5-9 years or 10 years or more (45.5%, 27.3%, respectively). No such significant large differences were found in the combined therapy group (p=.984).

Type of therapy	**Indicator**	**Duration of epilepsy**				**Total**
		One year or less	**1.5-4 year**	**5-9 year**	**10 year or more**	
Fit not controlled	Count	9	20	12	16	57
	Percentage	15.8%	35.1%	21.1%	28.1%	100.0%
Fit controlled	Count	14	28	8	6	56
	Percentage	25.0%	50.0%	14.3%	10.7%	100.0%
Total	Count	23	48	20	22	113
	Percentage	20.4%	42.5%	17.7%	19.5%	100.0%

p= .05

Table 3: The distribution of control of epileptic fit in epilepsy by the duration of epilepsy in

Al-Hussieny Teaching hospital in holy Kerbala and Medical city in Baghdad/Iraq in 2018 (n=113)

The most frequently used drugs in the total epileptic patient were Sodium Valproate and Levetiracetam (figure 3).

Next step in the analysis was to try a logistic regression mode for fit control and its potential predictors.

The results showed that the highest significant regression coefficient was for the type of treatment (4.45, p<.001). Next was the type of fit (2.22, p=.107).

Further analysis was to assess the simultaneous effect of each predictor in Structural Equation Model for fit control which showed that the highest weight for regression coefficient was for the type of treatment followed by fit type (figure 3).

Figure 3: The Structural Equation Model for fit control with its potential predictors in in Al-Hussieny Teaching hospital in holy Kerbala and Medical city in Baghdad/Iraq in 2018 (n=113/Iraq in 2018 (n=74)

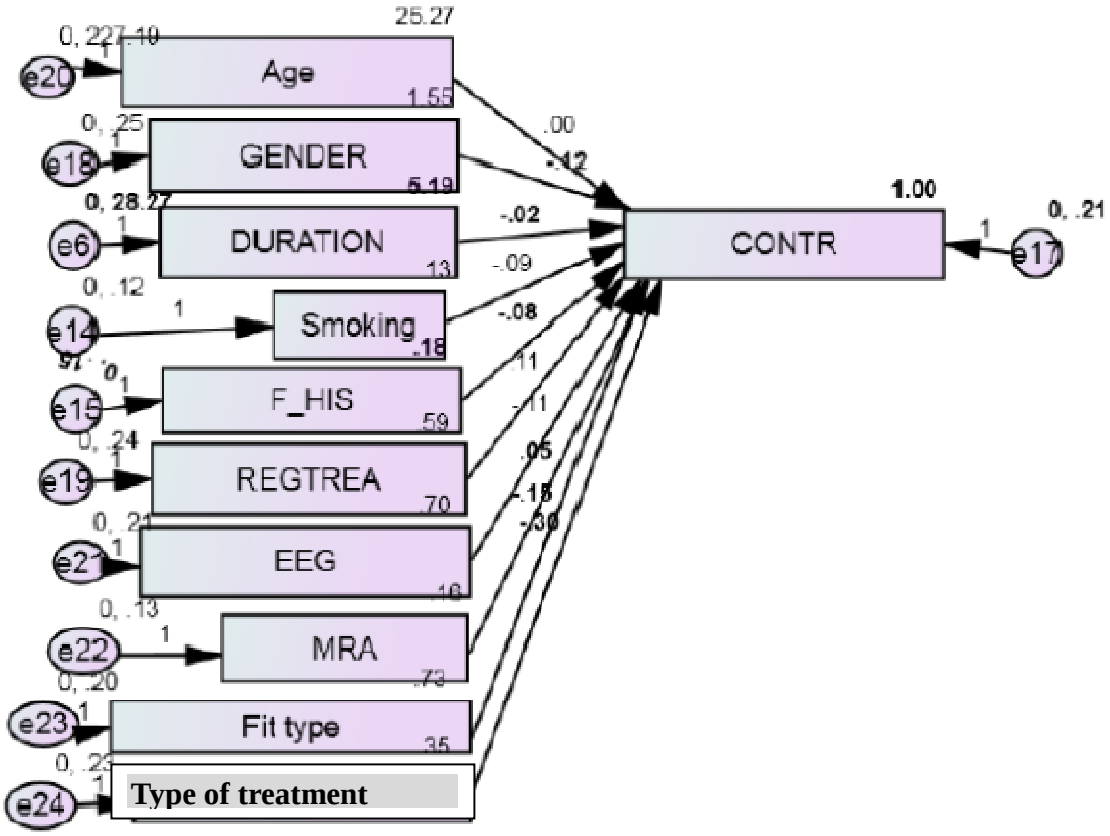
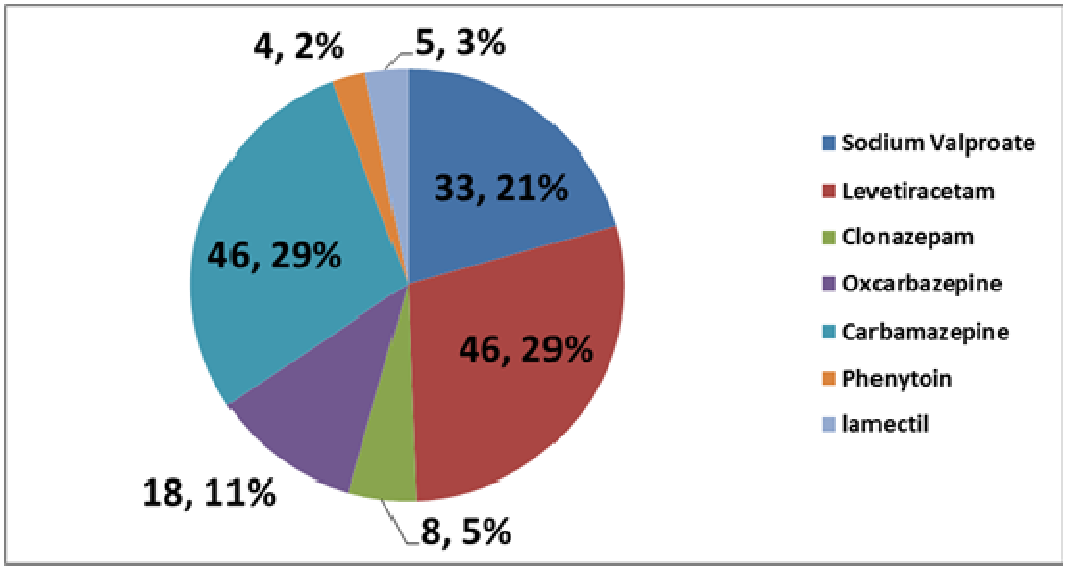
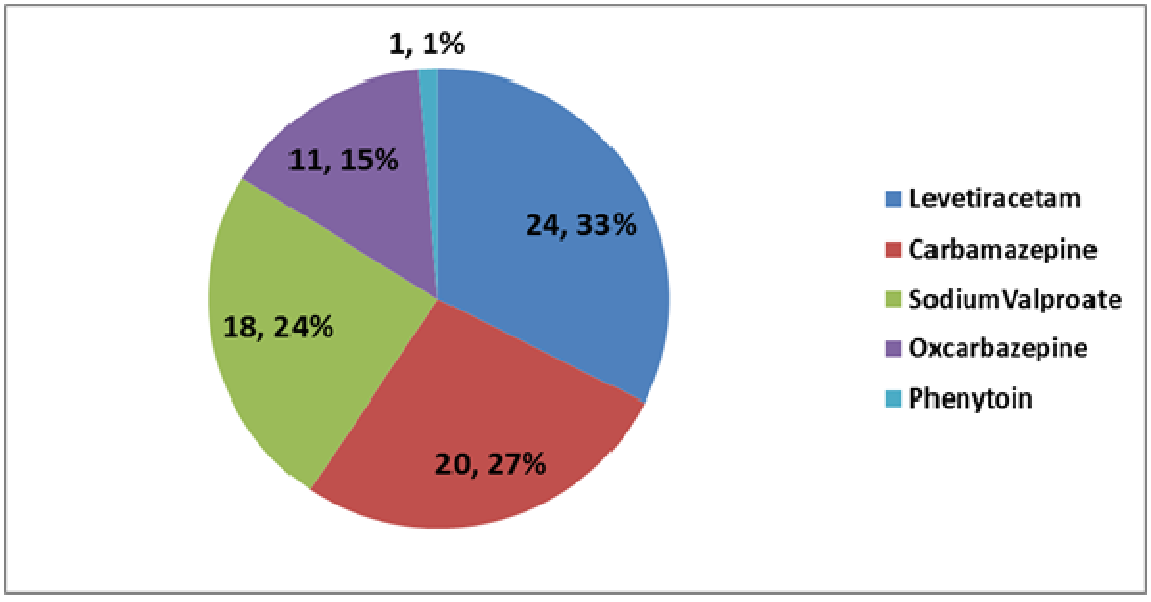


Figure 4: The distribution of type of drug taken by all the epileptic patients in Al-Hussieny Teaching hospital in holy Kerbala/Iraq in 2018 (Freq., percentage, total is 160 as two thirds used combination therapy)



When the type of treatment was explored within montherapy group of patients alone Levetiracetam was the main drug used (24 patients) followed by Carbamazepine (20 patients, figure 4).

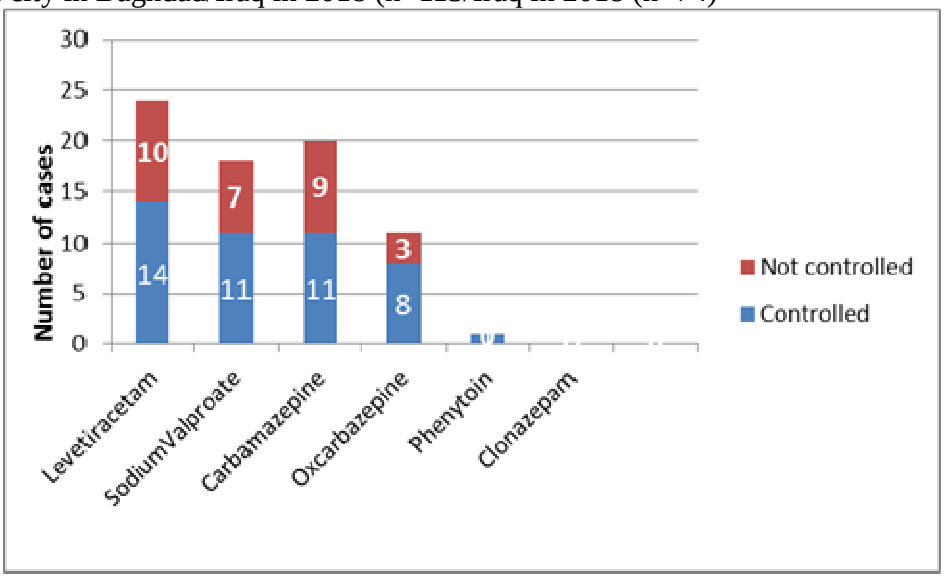
Figure 6: The distribution of type of drug taken by the epileptic patients in the monotherapy group in in Al-Hussieny Teaching hospital in holy Kerbala and Medical city in Baghdad/Iraq in 2018 (n=113/Iraq in 2018 (n=74)



The results of treatment of epileptic patients as determined by controlling epileptic fit was determined only in the monotherapy group as the possible potentiation in the combined therapy group could not be determined (12). The analysis for monotherapy showed that best results were achieved with Levetiracetam where about one third were controlled while only one quarter of those taking Sodium Valproate or Carbamazepine were controlled

(figure 5). However, these results could not be a firm indication for drugs potency for the small number of patients in the sample and for the great number of confounders in determining drug effect.

Figure 5: The distribution of epileptic fit control by the type of drug taken by the epileptic patients in the monotherapy group in in Al-Hussieny Teaching hospital in holy Kerbala and Medical city in Baghdad/Iraq in 2018 (n=113/Iraq in 2018 (n=74)



Discussion

The results of the present study showed that monotherapy was more successful in achieving epileptic fit control for at least six months in nonresponsive epileptic patients in tertiary neurology centers in Iraq (table 1). Most reviewed literatures stressed that montherapy is the first choice in epilepsy treatment and combined therapy should be reserved for especial occasions of strict indications (14-18). In Iraq a cross sectional study among 52 patients with epilepsy in Sulaymania city in 2013 reached a conclusion that monotherapy was effective and safe and showed higher control rate (95% vs. 91% (17). Similarly, a study among 257 case in Baghdad concluded that monotherapy was the main (75% of patients) used therapy (32).

Too many references stressed that monotherapy is the main line of therapy and as a preferred initial management approach in epilepsy care, since most patients are successfully managed with the first or second monotherapy given. Suggested alternative approaches when patients fail monotherapy include substituting a new AED monotherapy, initiating chronic maintenance AED combined therapy, or pursuit of non-pharmacologic treatments such as epilepsy surgery or vagus nerve stimulation (13, 20). A noteworthy point in favor of monotherapy is the fact that in developing countries there are greater economic constraints on prescribing and fewer drugs are available (17).

The present study results showed that, in monotherapy group, best results as suggested by controlling the occurrence of fit was obtained by Levetiracetam followed by Sodium Valproate or Carbamazepine (figure 5). A similar finding was reported in a study among a random sample of 52 patients with epilepsy in Sulaymania city/Iraq in 2013 compared using Levetiracetam as a monotherapy with combined therapy in the treatment of

generalized and focal epilepsy (17).

The results of the present study did not permit comparison and analysis of specific combinations of drugs due to the small sample size. A review study of twenty trials favored Oxycarbamazepine, Carbamazepine, and lamotrigin as the best combination of tolerability and seizure control, of which Oxycarbamazepine and Carbamazepine provide the best fit control and lamotrigin best tolerability resulting in a lower treatment failure rate (25). The problem in Iraq is that the patients need to pay for the drugs which are costly, especially for lamotrigin. However, a recent Cochrane systematic review found that levetiracetam performed (statistically) significantly better than both current first-line treatments carbamazepine and lamotrigin (1).

In the present study about two thirds (59.3%) were taking medication regularly and the addition of multiple drugs did not affect patients' compliance (table 1), and compliance was only associated with age category and duration of disease. Similar findings were reported by a study in Sulaymania/Iraq in 2010 among two hundred patients with epilepsy patients less than 18 years of age. It showed that drug compliance was satisfactory in 123(62.5%) and was poor in 77(37.5%) of the patients according to their self or parental report. Age of the patient, gender, residence, etiology of epilepsy, and monotherapy versus combined therapy did not significantly influence the drug compliance but duration of the disease, parental education, family size and positive family history of epilepsy were more significantly associated with drug non-compliance (28).

The duration of disease was a significant predictor of treatment success in the present study and was encountered in about two thirds of the patients suffering from epilepsy for less than five years compared to one quarter to one half of those with epilepsy for longer period (table 3). This finding was almost similar to that reported in the study among epileptics in Sulaymania /Iraq where durations was significantly associated with patients' compliance (28).

Conclusions

This study is among the few Iraqi published studies investigating epileptic patients treatment including most recent items used in epileptic therapy. Additional strength is the inclusion of two different tertiary care centers with acceptable number of patients.

Two main findings were noteworthy in this study. The first is that monotherapy is better than combined therapy in reaching fit control in epileptics, and the second the positive association of control with the duration of disease and positive family history.

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