Review of Epilepsy

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1. Introduction

Epilepsy is one of the most common and chronic neurological conditions. It is estimated that epilepsy affects 65 million individuals regardless of their gender, age, and socio-economic status worldwide. Infants and the elder have the highest risks. One-third of epilepsy is generalized and two-third is focal (Burakgazi and French, 2016).

The prevalence of epilepsy in developing countries is higher than in developed countries (van Diessen *et al.*, 2018). Epilepsy is associated with increased mortality and physical and psychological comorbidities. The mortality rates in developed countries are 1.6-3.0 times higher than the general population. The mortality rates in developing countries could increase to 7.2 times (Hamilton *et al.*, 2020).

Epilepsy patients normally require lifelong medications to control the seizure.

Epilepsy not only affects the individuals in their education, occupation, and social relationship but also increases the financial burden of the individuals, family, and society.

Epilepsy is a disease characterised by unprovoked recurrent seizures and meets one of the following three conditions (Fisher *et al.*, 2014),

1. At least two unprovoked or reflex seizures occurring more than 24 h apart
2. One unprovoked or reflex seizure with a high risk (over 60%) of further seizures similar to the general recurrence risk after two unprovoked seizures, occurring over the next 10 years
3. A diagnosed epilepsy syndrome

The risk of the second seizure after the first one decreases over time. About 60% to 70% of the second seizure occurs within 6 months after the first seizure. 34% of the cases with first seizures become epilepsy patients within 5 years. The following is the list of possible causes of seizures(Legg and Newton, 2017)

- Remote brain injuries
- Acute brain injuries
- Metabolic derangements
- High fever
- Significant sleep deprivation
- Medications
- Withdrawal from alcohol or drugs
- Excessive intake of alcohol
- Unknown reasons

Epilepsy is considered to be resolved when

1. Patients have age-dependent epilepsy syndrome and are older than that age.
2. Patients are seizure-free at least 10 years without taking AED medication for at least 5 years.

2. Classification of Seizures and Epilepsy

Figure 1 is the new epilepsy classification framework updated by The International League Against Epilepsy (ILAE) to classify epilepsy in different clinical environments. This framework starts with classifying the seizure type. Seizures can be divided into 1) focal, 2)generalized and 3)unknown type. The second level is to identify the epilepsy type which includes 1)focal, 2)generalized, 3)combination of generalized and focal and 4)unknown. The third level is to diagnosis Epilepsy Syndromes which are the features associated with the type of epilepsy and can be seen simultaneously from EEG recording and scanned images. The aetiology of the patient's epilepsy should be identified when the patients' first seizure is observed. Epilepsy patients are also associated with comorbidities such as learning, motor deficits, and motor disorder problems(Scheffer *et al.*, 2017). The seizure onset is known as where a seizure starts. Figure 2 is the ILAE 2017 classification of seizure types' basic version.

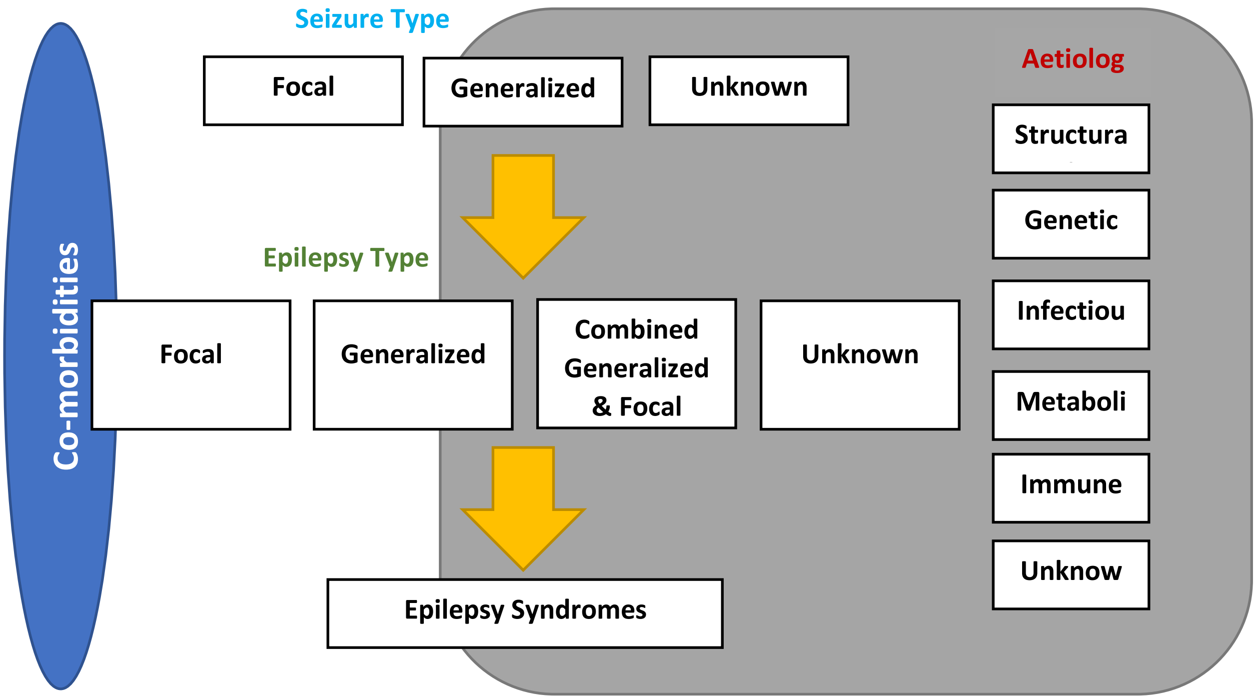


Figure 1: Classification of seizure and epilepsy (Scheffer et al., 2017)

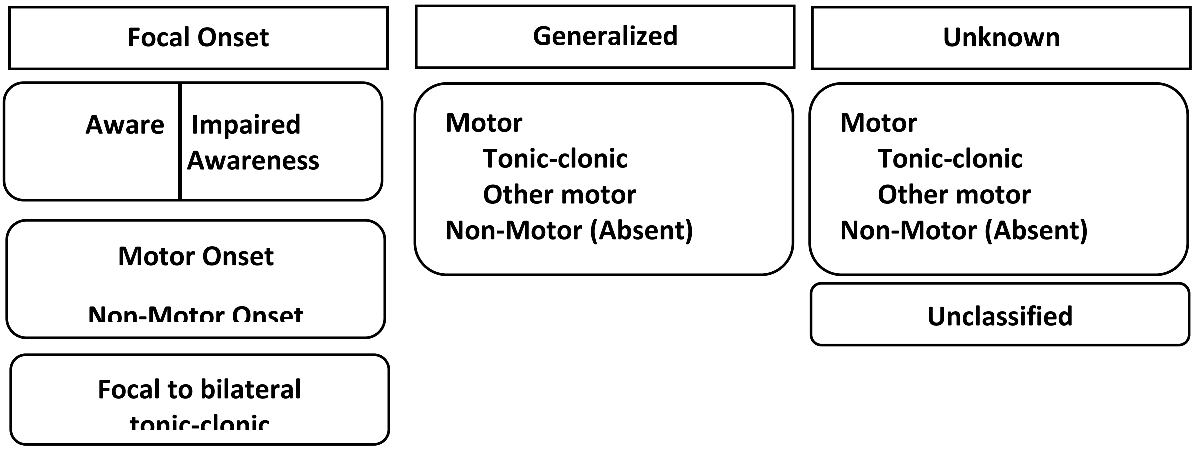


Figure 2: ILAE 2017 classification of seizure types basic version

3. Treatment

It is a challenge for the clinicians to choose the suitable treatment option for epilepsy. In the United States, more than twenty anti-seizure medications and two implantable devices are commercially available. Recently, several epilepsy treatments have been proposed and tested, such as dietary therapy, vagus nerve stimulation technology(Shih *et al.*, 2017).

The treatment outcomes of epilepsy can be one of the following,

1. early and persistent seizure freedom,
2. delayed but persistent seizure freedom,
3. the fluctuation between periods of seizure remission and relapse, and
4. no seizure freedom.

Seizure freedom is when the patients have no seizures for at least 12 months (Brodie *et al.*, 2012).

AED is the first line and mainstay treatment for the newly diagnosed epilepsy patients. Other interventions of epilepsy include surgery, Vagus nerve stimulation, deep brain stimulation, ketogenic diet, and change of lifestyle. Epilepsy treatment aims to control and stop the seizure to achieve seizure freedom. (Sørensen and Kokaia, 2013; Tang, Hartz and Bauer, 2017; Duncan *et al.*, 2006)

3-1. Anti-epileptic drugs (AEDs)

Anti-epileptic drugs (AED): AEDs are the main treatment that can achieve seizure freedom or satisfying control seizures. AEDs tend to prevent seizures by reinforcing inhibition or attenuating the excitation of neuronal hypersynchrony. There are four types of AEDs based on their targets,

1. intrinsic voltage-gated ion
2. GABAergic inhibition,
3. glutamatergic excitation, and
4. neurotransmitter release

Each AED prevents seizures in its specific way(Kim *et al.*, 2020).

However, there exists a gap in the subspecialty to provide the best option for the seizure. For example, the FDA in the United States uses randomized controlled trial and meta-analyses studies to evaluate and assess the effectiveness and safety of anti-seizure drugs for the patients. However, these studies normally exclude the patients who have other significant medical conditions and the guidelines based on these studies might not be applied to some patient groups, such as the elderly (Shih *et al.*, 2017).

3-1-1. The treatment process of AEDs

Table 1 summaries of the steps of AEDs treatment to a newly diagnosed epilepsy patient(Chen *et al.*, 2018; St and Erik, 2009a).

Table 1: Example of Steps of AEDs treatment to a newly diagnosed epilepsy patient

Stage	Treatment
Diagnose	• two or more seizures or • one seizure with a clear high risk of recurrent seizure
Newly diagnosed epilepsy	• start with monotherapy at a low dose • Select AED based on ➢ the diagnosed epilepsy syndrome ➢ patient characteristics, such as age, gender ➢ Comorbidity and co-med • Affordable
Switching to different AED or polytherapy	When the initial AED • cannot achieve seizure remission • induce intolerable adverse effects • one or more monotherapy fails to control seizures
Go for other treatment options	at least two or three AEDs (in monotherapy or polytherapy) fail to control seizures
Withdraw AED or reduce the bose of current AED	Remain seizure-free at least 2 years • Risk of seizure relapse

3-1-2. Withdrawal of AEDs

About 70% of patients by the usage of AEDs treatment will go into prolonged terminal seizure remission. All AEDs can induce dose-related adverse effects such as drowsiness, fatigue, dizziness, blurry vision, and incoordination, etc, which will affect the quality of life. So to continue or discontinue AEDs treatment is a trade-off between long-term adverse effects and seizure relapse and the concern of unnecessary treatment. Withdrawl from AEDs in remission has been done by many patients.

The patients of withdrawal AEDs can improve the overall quality of life at the expense of a higher risk of seizure relapse compared to those remaining in the treatment. The relapse rate is the highest in the first 6 months after withdrawal AEDs and decreases dramatically over time. The risk of seizure relapse after the reduction of AED dose or withdrawing AEDs is associated with prolonged periods of seizure-free. It is suggested that to withdraw from AEDs after more than 5 years of seizure remission won't increase the risk of seizure relapse (Wang *et al.*, 2019; Schmidt and Sillanpää, 2017). Table 2 lists the factors of favourable outcome and risk factors of withdrawal outcomes for the adult and children.

Table 2: the factors of favourable outcome and risk factors of withdrawal outcomes for the adult and children

Factors related to favourable outcome after withdrawal	Risk factors for relapse for children
• Seizure freedom for more than 2 years • Seizure freedom achieved by one drug at a low dose • No unsuccessful attempts of withdrawal • Normal neurological exam and EEG Generalized epilepsy type except for JME • Develop epilepsy syndromes	• The onset of epilepsy at an older age • Remote symptomatic aetiology • Specific syndromes (e.g. JME particularly after short remission) • With a family seizures history • History of (atypical) febrile seizures • History of neonatal seizures • Multiple seizure types • Mental retardation • Abnormal neuroimaging • Polytherapy • EEG abnormalities

The factors to be considered to choose the first AED are its efficacy, tolerability, cost, gender, age, ease of use, toxicity, comorbidities, and con-meds.

Around 50% to 60% of the newly diagnosed epilepsy patients have positive responses to the first AED. 10%–15% can also achieve seizure-free by AED treatment after a series of trials and errors within 2 to 5 years. However, 30% of patients are drug-resistant (refractory epilepsy) and cannot control their seizure by AED treatment. AED resistance is often seen in temporal lobe epilepsy patients who have seizures originating from the temporal lobe.

3-1-3. Refractory Epilepsy

Epilepsy with seizures that cannot be controlled by at least two or three AEDs is considered as refractory epilepsy. Refractory epilepsy is associated with higher morbidity and mortality rates, devastating psychosocial consequences, serious cognitive problems, and impaired quality of life. Those who failed the first drug have a lower chance to become seizure-free with the different drug follow-up trials.

Refractory Epilepsy remains a major problem and challenge for epilepsy management since the AEDs became available. (Kwan and Brodie, 2000) suggested that patients are more likely to have refractory epilepsy if they experience more seizures before the treatment and have uncontrolled seizures after the first AED treatment. Their study found that

- 63% of patients became seizure-free (57% never received AEDs before, 6% otherwise)
- The response to the first AED is a powerful factor to predict refractory epilepsy.
- Among those who never received AEDs before, 47% became seizure-free after the first AED treatment. 13% became seizure-free after the second AED treatment (monotherapy). 1% became seizure-free after the third AED treatment (monotherapy). 3% became seizure-free with 2 dugs treatment.
- Patients with structural cerebral abnormality have a higher risk to have refractory epilepsy than patients with idiopathic epilepsy.
- Patients might have refractory epilepsy from the beginning.

As only less than 10% of refractory epilepsy patients might become seizure-free by surgery, AEDs treatment is still an option for refractory epilepsy. Polytherapy is a treatment option for patients without other alternatives. However, polytherapy is associated with adverse effects, decreased patient compliance, deteriorated quality of life, and increased cost. In the abovementioned study, only 3% of patients become seizure-free with 2 drugs treatment. A more effective combination of AEDs might improve the outcomes. The following is the concept of rational prescription of polytherapy (Kim *et al.*, 2020; St and Erik, 2009b)

- A combination of AEDs with different mechanisms of action is more effective than polytherapy with similar or overlapping mechanisms of action
- Interactions between the drugs should maximise the efficacy and minimise the adverse effects
- Prescribe the constant dose of the current AED and increase the new AED slowly and gradually to the optimal dose
- The ratio between prescribed daily doses and defined daily doses should not exceed 2 to minimise the neurological side effects
- Reduce the number of AEDs to reduce the likelihood of pharmacokinetic and pharmacodynamic AED interaction
- If an adverse effect develops during titration of the newest AED, reduce the dose of the least effective one to increase tolerability
- Increase the dose of the newest AED and decrease the dose of ineffective AED simultaneously

3-2. Surgery

Surgery: Surgery is an option for AED resistant patients with focal epilepsies. The surgery intervention removes the part of the brain which causes seizures. 80% of post-surgical patients can achieve seizure-free.

Before the surgery, there are several pre-surgical assessments to evaluate the potential outcome of the surgery. First, the region of resection should not result in major neurological compliance. Two-phase tests will be performed to ensure that surgical intervention is the best option for the patients. Phase 1 test is a non-invasive test. Phase I attempts to identify the region of resection, evaluate the safety of removing region, and predict the outcome of the surgery. This test includes

- EEG: This test not only diagnoses epilepsy but also investigates the types of epilepsy, partial or generalized epilepsy. During EEG recording, the patients might not have the seizures. But epileptic activities can be observed in EEG recording.
- Inpatient Video-EEG monitoring: In this test, both video and EEG are acquired simultaneously. The symptom and EEG change during the seizures are analysed. EEG between seizures is also analysed to identify the region where seizures originate.
- MRI: MRI can detect abnormality within the brain and identify the cause of epilepsy, lesional epilepsy, or non-lesional epilepsy.
- PET: PET scans are used to investigate the metabolic activities within the brain. For epilepsy patients, the activities in the region where the seizures originate are expected to increase with seizures present and decrease without seizures present. PET scan might show abnormalities where MRI does not.
- SPECT: When seizures occur, the amount of blood flows to the region where the seizures originate increase. SPECT scans during the seizures can confirm the region where the seizures begin.

- fMRI: fMRI is used to assess cognition function of language and function and predict potential post-surgery cognitive deficit. The test identifies the dominant side of the brain for language and checks if the memory function in the epileptic region is affected.
- Wada test, Intracarotid amobarbital/methohexital: This test is similar to fMRI for an independent test of cognitive function language and memory in one of the half brain. This test is also used to predict post-surgery cognitive deficits.

These tests are to locate the region where the seizures originate. If the epileptic region from different tests is the same, the patient is a potential candidate for undergoing the surgery. In some cases, phase II evaluation might be required. This evaluation implement the electrodes on the surface of the brain or inside the brain to identify the exact location where seizures originate in the brain.

- Video-EEG monitoring: It is a similar setup and analysis as Phase I. But it is stereo-EEG used instead of sEEG.
- Functional Mapping: This test is to determine if there are overlapping areas in the region of resection with the critically important area of the brain to reduce and minimise the potential deficit after surgery

Although surgical intervention for temporal lobe epilepsy has shown its clinical benefits compared to the continuous use of AEDs and is recommended as a treatment option to refractory temporal lobe epilepsy. However, not all refractory epilepsy patients are suitable for this treatment. Only less than10% of refractory epilepsy patients suitable for surgery. Due to surgical cost and therapy after the surgery, it is only considered as the last option for patients with severe AED resistance.

3-3. Vagus nerve stimulation

When surgery is not possible, Vagus nerve stimulation can be an option. Vagus nerve stimulation might not be able to achieve seizure freedom but reduce the severity and the frequency of seizure. The simulation device is connected to the vagus nerve in the neck. However, it has some side effects, such as hoarseness, sore throat, and coughing. 30% to 40% of patients can expect a 50% reduction in seizures through this treatment.

3-4. Diet and change of lifestyle

The ketogenic diet has been used to treat epilepsy since 1920 before AEDs are available. The ketogenic diet is a high fat, low carbohydrates, and adequate protein diet. It is a treatment option for children but adults with refractory epilepsy. This option has shown that 50% of the patients can reduce 50% of seizure numbers. However, such a diet is associated with several adverse effects. It also requires the supervision and guidance of the dietitians. The Modified Atkins diet is similar to the ketogenic diet with less restriction.

Several factors have been identified to increase the risk of seizure for epilepsy patients, including, stress, tension, fatigue, sleep deprivation, consumption of substances in alcohol, caffeine, and nicotine, abuse of drugs, etc. Seizures can be controlled by reducing the seizure risk factors and triggers through the change of lifestyle. A healthy lifestyle can improve control of the seizures.

4. Cost

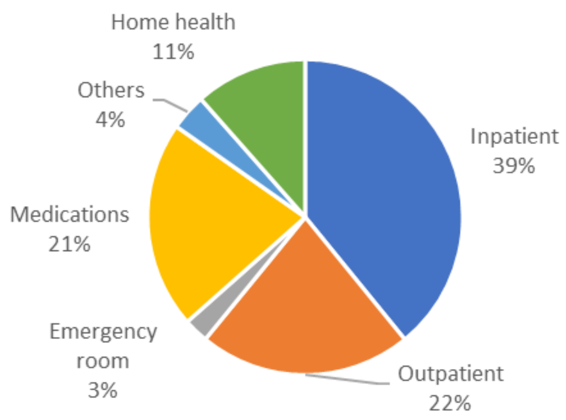
It is difficult to estimate the costs of epilepsy as patients have different seizure frequency, various seizure types, degree of severity, and the outcome of the treatment. Seizure frequency is the main factor correlated with healthcare utilization(Ip *et al.*, 2018).

4-1. United States

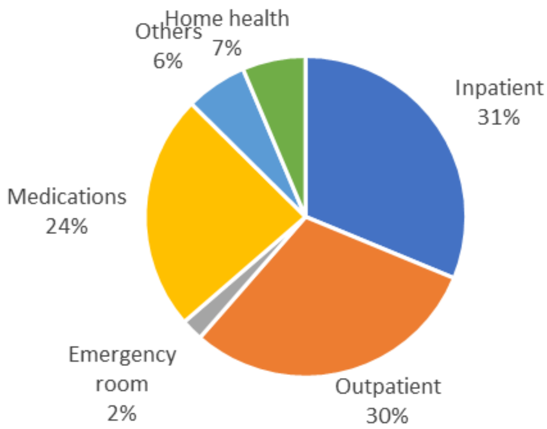
(Lekoubou, Bishu and Ovbiagele, 2018a)evaluated health care expenditures among the elderly (aged ≥65 years) patients with epilepsy from 2003 to 2014 in the United States. The total health care expenditures include the expenditures for inpatient hospitals, hospital outpatient, prescription medicine, emergency room, home health care, and other medical-related.

The adjusted average total health care expenditures per person per year for the elderly with epilepsy were $ 12,526, 13, 423, and 10.569 for 2003-2006, 2007-2010, and 2011-2014 respectively. The adjusted average total health care expenditures per person per year for the elderly without epilepsy were $ 6,893, 6,501, and 6,205 for 2003-2006, 2007-2010, and 2011-2014 respectively. On average, total health care expenditures of the elderly with epilepsy higher than the one of the elderly without epilepsy. The mean percentage of each unadjusted expenditure across three periods is shown in figure 3.

The mean annual aggregate direct cost of epilepsy in the elderly was $7.8 billion between 2003 and 2014. Compared to the elder without epilepsy, the incremental cost was $2.1 billion.



(a) Percentage of expenditure for the elder with epilepsy



(b) Percentage of expenditure for the elder without epilepsy

Figure 3: Percentage of each expenditure, (a) elder with epilepsy and (b) elder without epilepsy

A similar study focused on the direct cost for children with epilepsy in the USA showed that from 2003 to 2014, the mean healthcare expenditure of children with epilepsy ($12,577) was almost 6 times higher than without epilepsy($2,024). The major contributions of the increased cost included the expenditures of the inpatient admissions, outpatient attendances, home healthcare, and medication (Lekoubou, Bishu and Ovbiagele, 2018b).

The annual unadjusted aggregate cost was $5.8 billion for the children with epilepsy which was $3.8 billion higher than without epilepsy.

4-2. France

A cohort study, from January 1, 2001, to December 31, 2013, which compared the cost-effective between surgery and medical treatments (Picot *et al.*, 2016). The participants of this cohort study were AED-resistant. They were divided into two groups based on the treatment choice of the patients. The operated group chose surgery to treat epilepsy and the medical group continued medication treatment.

In the second year, 69% of the operated group and only 12.3% of the medical group were seizure-free. In the fifth year, 76.8% of the operated group and only 21% of the medical group achieved seizure freedom.

The direct cost of the operated group became lower than the medical group from the second year after the surgery. The reduction in the cost of the operated group came from the cost of AEDs and hospital utilization Although it was recommended to continue AEDs after the surgery, the amount of AEDs for the operated group was lower. The mean cost of the pre-surgery evaluation was € 7,784 for the operated group. The mean cost of pre-surgery evaluation and surgery was €21,517.

4-3. Germany

(Strzelczyk *et al.*, 2017) evaluated the cost of the patients suffering from severely drug-refractory epilepsy. The data used in this study covered the insurance year from 2008 to 2013. In this study, the patient was prescribed at least four AEDs within 18 months was classified as a severely drug-refractory epilepsy case.

During the 3-year follow-up study period, on average, each patient was prescribed 5.3 AEDs. The mean time between the prescription of the first three AEDs and the fourth AED was 212 days. The mean hospital admissions related to epilepsy per patient were 2.8 times with a mean stay of 10.5 days per admission.

On average, the annual direct cost of the 3-year follow-up ranged from €12,925 and €14,639 which was higher than €3,011, the annual average cost for insurants in Germany. The annual inpatient treatment costs contributed 37% to 42% of the direct cost. Annual medication costs, on the other hand, contributed 35% to 38%.

A cohort study in Germany estimated the changes and trends of direct and indirect costs of epilepsy patients over the time in the year of 2003, 2008, and 2013 at the same medical centre (Willems *et al.*, 2018).

In 2013, the average direct cost was €1879 per patient per three months. The expenditures of AEDs and hospitalization were €786(42%) and €785 (42%) respectively which occupied over 80% of the total direct cost. The other expenditures included rehabilitation (€118, 6%), diagnostic workup (€47, 3%), outpatient care (€109, 6%), and physical treatment (€33, 2%).

Total direct costs of 2003 and 2008, after adjusting to 2013, were €1355 and €1823. The percentages of AEDs and hospitalization were 59%, 28% in 2003, and 34%, 47% in 2008. Both expenditures were the main sources of the direct cost as in 2013.

The estimation of the indirect cost was based on the patients aged 65 or younger. In 2013, the average indirect cost was €1795 per patient per three months. Early retirement, €994 (55%), was the largest part of the total indirect cost, followed by the loss of productivity €801 (45%).

The total indirect costs of 2003 and 2008, after adjusting to 2013, were €1862 and €2069. The percentages of early retirement in the year 2003 and 2008 were 48% and 46%. The portions of loss of productivity were 52% and 54% in 2003 and 2008 respectively.

This study also demonstrated that the cost of AEDs was a major contributor to the direct cost.

4-4. UK

(Juarez-Garcia *et al.*, 2006)reported the estimated cost of epilepsy misdiagnosis in England and Wales in 2002. The cost of epilepsy misdiagnosis was £316. The portion of inpatient admissions, inappropriate prescription of AEDs, outpatient hospital visits, and GP visits were, 45%, 26%, 16%, and 8% respectively. The annual aggregate medical cost for misdiagnosis was 29 million.

4-5. Spain

(Pato-Pato, 2013) invested the medical cost and non-medical cost of epilepsy patients in Spain. The medical costs included all expenditures related to epilepsy, such as primary care, A&E visits, inpatient admissions, various diagnostic tests (EEG, CT, MRI, etc), outpatient administration, prescription, visits of neurology specialists, etc. Non-medical costs included the transportation of hospital visits, psycho-educational support, and social support. This study was based on the data of 171 patients in 2008.

The result showed that the annual mean cost of AED, visits of GP, neurologists, A&E, and hospitalisations, and the diagnostic test was €1027, €644, and €349 per patient. The total medical cost per year was 2020. The mean annual non-medical cost was €90 per patient.

AEDs were the major contribution of the total medical cost. The mean annual direct medical cost without AED was €993 which was higher than €648, the average annual cost per patient in Spain health service.

In general, the cost of the first year is the highest compared to the following years. The cost decreases dramatically over time (Begley and Beghi, 2002). For example, in the USA, 4.5, 6.7, and 7.7 times of years 2, 3, and 4 respectively. In the UK, the first-year cost is 3.25 and 3.61 times the costs in years 4 and 8. In France, the first-year cost is 3.8 times of year 2. The pattern of reduced cost in time is similar.

5. EEG role in Epilepsy Management

EEG is useful for confirmation, classification, and localization of epilepsy. EE can help to answer the following three important questions in epilepsy diagnose,

- Does the patient have epilepsy?
- Where is the epileptogenic zone? and
- How good is therapy?

Interictal epileptiform discharges (IEDs) and abnormalities in EEG help to differentiate between epileptic and other nonepileptic paroxysmal attacks. “Epileptiform” indicates/implies EEG patterns that are associated with a high risk of having epilepsy. EEG is normally delineated into ictal (during a seizure), interictal (between seizures), and postictal (after a seizure), representing the time when the seizures start and stop. This is important to understand the seizures as seizure might be the result of interictal states(Fisher, Scharfman and DeCurtis, 2014).

About 10% of epilepsy patients have normal EEG without IED. IED can also be found in a small portion, 0.5% in adults and 2% to 4% in children, of normal subjects and individuals with neurological disorders not related to epilepsy. The chance for healthy subjects with IEDs developing epilepsy is 2% to 3% For epilepsy diagnose, EEG has low sensitivity, 25% to 56%, and better specificity, 78% to 98%. Factors can affect IED shown in patients' EEG (Noachtar and Rémi, 2009; Smith, 2005).

- Age: Children are more likely to show IED in EEG than adults.
- Seizure type, syndrome, and location: Temporal lobe epilepsy is more likely than epileptic foci in the mesial and basal cortical regions.
- Seizure frequency: repeated seizures are more likely than rare.
- Timing of recording: Recording EEG within 24h is more likely than later (51% vs 34%).
- Some patients might show IEDs mainly in sleep. Patients' co-med might also affect IDE as the medicine might increase or reduce IEDs.

IED can be found in the first EEG test in 50% of epilepsy patients. Yield in adults can be improved by the routine repeated EEG, combination of sleep, and wake-up EEG.

Several EEG patterns have been regarded as IEDs. Some of them can be used to identify specific epilepsy syndromes. Table 3 lists EEG patterns of IEDs and the associated epileptic syndromes (Noachtar and Rémi, 2009).

Although EEG has demonstrated its usefulness as an aid to diagnose epilepsy is established, it has limited use to assess the effectiveness of treatment. For example, there only exists a weak association between the amount of IEDs and seizure frequency. The effects of AEDs on IEDs are different.

Table 3: EEG patterns of IEDs and the associated epileptic syndromes

EEG pattern	Associated Epileptic syndrome/aetiology
Spikes:Anterior temporal spikes	Mesial temporal lobe epilepsy
Generalized 3-Hz spike-wave complexes	Absence epilepsy
Polyspikes: Generalized polyspikes Regional (extratemporal) polyspikes	 Juvenile myoclonic epilepsy Focal cortical dysplasia
Spike-wave complexes: >4-Hz spike-wave complexes	 Juvenile myoclonic epilepsy
Generalized slow spike-wave complexes	Lennox–Gastaut syndrome
Hypsarrhythmia	West syndrome
Sharp waves	-
Benign epileptiform discharges of childhood	-

From the above, there are several problems in epilepsy management, such as the cost of AED, refractory epilepsy, etc. EEG might be a useful technique to improve epilepsy management, including prediction of the recurrent seizure, prediction of AED treatment outcome, prediction of the outcome of the surgery, and estimation of the time to withdraw AEDs.

5-1. EEG after First Unprovoked Seizure

The usefulness of EEG to predict seizures after the first unprovoked seizure remained debatable due to the difference in terms of study design, groups of the patients and age etc. (Schreiner and Pohlmann-Eden, 2003)evaluated the usefulness of standard EEG and sleep-deprived EEG on the prediction of recurrent seizure after the first unprovoked seizure. In this prospective, hospital-based study, the first EEG of 157 patients was recorded within 48 hrs after the first seizure. They found

1. Over 70% of patients with first unprovoked seizure showed EEG abnormal activities, focal abnormalities (36.9%), focal epileptiform activity (17.2%), generalized epileptiform activity (9.6%) and diffuse slowing (7.0%). Among these abnormities, focal epileptiform activity and focal abnormalities were associated with a higher risk of recurrent seizures, followed by the abnormalities of generalized epileptiform activity and diffuse slowing.
2. Standard EEG was more sensitive to detect abnormality than clinical assessments. The abnormality was found from 71% of the patients in the first EEG, and only 40% in the neurologic assessment. EEG abnormality was detected in 60 patients out of 94 who were normal in the neurologic assessment.
3. Seizure recurrence: 49 (31.2%) of patients had a recurrent seizure. For all patients the risk of concurrent seizures in 6 months, one year and two years were 23.1%, 27.5%, and 31.0% respectively but the patients with abnormal EEG were associated with significantly higher risk over time.
4. Sleep deprivation EEG: 48% of patients showed abnormalities in sleep deprivation EEG. The authors suggested that the possible explanation is that the interval between the first seizure and Sleep EEG recording was longer than 48 hrs. The epileptic excitability might lose over time. Sleep deprivation EEG detected abnormal activities in 9 patients while they were normal in routine EEG. 3 of them were also normal in standard EEG. Sleep deprivation EEG did not detect the abnormality in 10 patients whose abnormalities were detected in standard EEG.
5. The authors suggested that early EEG after the first seizure was a valuable and useful predictor for seizure recurrence. Sleep deprivation EEG might be also useful to detect additional abnormalities which were not detected in the standard EEG.

5-2. Related Works and EEG Features in Automation Detection

EEG interpretation mainly relies on experienced EEG-ers. Manual EEG interpretation is time-consuming, expensive and subjective. Automated EEG interpretation process is not only faster and flexible but also provides responsive result in real-time. Several studies had proposed algorithms to automate the detection process. These algorithms normally consisted of machine learning models as the classifier with extracted EEG features based on the types of problems in different domains.

5-2-1. Time-domain

(Tessy, Shanir and Manafuddin, 2016) used two EEG features from the time domain, line length and energy, as the features to classify epilepsy. The line length and energy in their work were defined as

Line length $$L = \frac{1}{N-1}\sum_{i=1}^{N-1}|x_{i+1} - x_i| \quad (1)$$ and

Energy $$E = \sum_{i=1}^{N} x_i^2 \quad (2)$$

Where x_i is EEG signal at index *i, N* is the total number of samples.

The features were applied to the classification methods, such as KNN, LDA and QDA. The result showed that using these two features, KNN outperformed LDA and QDA methods with the accuracies of 100% and 94.4 % of two different classification tasks.

(Sharmila and Geethanjali, 2020) extracted more time-domain features from EEG and D3-D5 & A5 coefficients of the discrete wavelet transform. These time-domain features included waveform length which was similar to line length reported in (Tessy, Shanir and Manafuddin, 2016), zero-crossing, and slope sign change. These features also included several statistics measurements, such as mean absolute value, standard deviation, and average power. The classifiers used in this study were naïve Bayes (NB) and support vector machines (SVM). The result demonstrated that time domain features extracted from discrete Wavelet transform were more robust and both classifiers achieved over mean accuracy 95% across different classification tasks.

However, as the datasets they used were artefact-free EGG with very small patient size. The setup required more evaluation before used in clinical practice.

5-2-2. Frequency Domain

(Faust *et al.*, 2010) estimated EEG power spectrum density by three different methods: autoregressive moving average (ARMA), Yule-Walker and Burg. From the power spectrum, 4 frequencies with the highest powers, local maxima, and least powers, local minima, were identified. The power and frequency of each local extrema formed a 1x16 vector which was used as a feature vector for classifiers Gaussian mixture model (GMM), artificial neural network (ANN), and support vector machine (SVM).

The result indicated that using classifier SVM by applying the features extracted from Burg's method outperformed the other combinations of feature extraction method and classifier. The specificity and sensitivity were 98.33% of 96.67%, respectively.

5-2-3. Time-Frequency Domain

(Tzallas, Tsipouras and Fotiadis, 2009) used power spectrum density extracted from several frequency bands within a window length as the features to detect epilepsy. In their proposed method, different time-frequency analysis techniques, such as short-time Fourier transform and Wigner-Ville distribution, were applied to EEG and calculated PSD within a specific time-frequency window as the features. The features were fed into different classification methods, such as ANN and k-NN classifier, to classify epilepsy. There were three classification tasks used to evaluate the effectiveness of the time-frequency feature, 1. normal and seizure, 2. normal, seizure-free, and seizure, and 3. Normal with eyes open, normal with eye closed, seizure-free, and seizure. The result showed the time-frequency analysis techniques with time and frequency smoothing windows can achieve better accuracies. The mean accuracies of these methods with smoothing time and frequency window were 98.8%, 99%, and 87.6% for the three classification tasks, respectively.

5-2-4. Combinations of Features from Different Domains

Some of the studies combined features from two or three of domains to automate epilepsy detections.

(Anusha, Mathews and Puthankattil, 2012) combined the features in the time domain, features in the frequency domain and the features derived from the time domain to identify epilepsy.

The time-domain features are the amplitude and duration of EEG half-wave. The first half-wave is the part which EEG rose to its peak and the second half-wave is the part which EEG went down. The average of amplitudes and durations of both half-waves within a specific window segment formed the time domain features, i.e. 4 features. In the frequency domain, the dominated frequency and average power were extracted. Seizures are found to have a recurrent component and present a dominant frequency. The features derived from the time domain were the slopes of first and second half waves and covariance of the durations in the first and second half-wave. As a result, there were 10 features in total.

Feedforward artificial neural network was used to classify EEG using these features. The accuracy rate of detection of normal EEG and epilepsy were 93% and 95%.

(Srinivasan, Eswaran and Sriraam, 2005) also (Schreiner and Pohlmann-Eden, 2003) combined the features in the time domain and frequency domain as the input of the artificial neural network to detect the epileptic activities. EED data were segmented into 1-second epoch to extract the feature. The selection of 1 second window length was to meet the clinical setup.

Three frequency domain features were dominant frequency, average power in the main energy zone, and normalized spectral entropy. The dominant frequency is the frequency with the highest power on the frequency spectrum. To get the average power in the main energy zone, average frequency (AF) of each epoch was found first by the equation (3)

$$AF = \frac{\sum_{i=1}^{N} Power_i \times f_i}{\sum_{i=1}^{N} Power_i} \qquad (3)$$

where i is the frequency component and N is the total number of frequency components. The main energy zone of each was defined as the frequency band centred at AF containing 80% of the total energy. Average power in the main energy zone was obtained by dividing the power in this frequency band by its bandwidth. The spectral entropy (SE) of the frequency range between f1 and f2 was defined by equation (4),

$$SE = \frac{\sum_{f_i=f_1}^{f_2} P_n(f_i)}{\log P_n(f_i)} \qquad (4)$$

The normalized spectral entropy (NSE) was equal to SE divided by log (N) where N was the total number of frequency components within the frequency band of f1, f2.

Two-time domain features were spike rhythmicity (SR) and relative spike amplitude (RSA). Before extracting these two features, the following pre-processing applied to raw EEG data.

1. The smoothing procedure was applied to EEG.
2. Original EEG data were subtracted by the smoothened EEG.

3. The absolute value of the difference EEG data was further denoised.
4. 50% of the maximum spike amplitude was used as the threshold to identify the peaks.

SR was defined as the number of spikes. RSA was the maximum amplitude of all identified spikes.

The classifier (ANN) was trained by using a different number of the features, from a single feature to 5 features. The result showed that single feature achieved the highest sensitivity and specificity with the overall accuracy of up to 99.6%.

Although EEG has demonstrated its effectiveness and usefulness as a diagnostic tool in many clinic applications such as sleep pattern classification, seizure prediction, and detection. However, EEG has its limitations,

1. Signal-to-noise ratios: EEG has low SNR. The desired brain activities are normally less significant than its background which includes environmental noise, spontaneous brain rhythms and signals resulted from some artefacts.
2. Non-stationary signal: its statistics characteristics vary over time which can affect the performance of the machine learning model trained by a limited amount of the data produced at a specific time interval.
3. Inter-subject variance: The different physiological characteristics across individuals can affect the performance of the classifier which has been trained by the data of limited subjects.

Some of the limitations can be resolved by processing pipelines with domain-specific approaches to clean the data, extract the desired features, and classify the data. However, pipelines can vary among different domains.

Furthermore, (Zhou *et al.*, 2018) and (Emami *et al.*, 2019) argued machine learning methods to detect seizures relied on hand-engineered features. As a result, feature selection and extraction are a fundamental step associated with the performance of classification. Also, these features and methods were only tested by a limited number of patients. These features might be subject-specific and cannot be applied to broader subjects.

Despite the effort for automated seizure detection, the current developments did not meet the requirement of the clinical applications. For example, four commercial seizure detection algorithms, CNet, Monitor, Reveal and Saab were tested by using the same datasets. The true positive rates vary from 71% to 76% and the false positives were 9.65 to 2.24 per hour. The performance is not acceptable for clinical practice (Golmohammadi et al., 2019; Biswal et al., 2017).

Deep learning has been proposed as a potential solution to improve generalisation capacities and flexible applications (Roy *et al.*, 2019). Compared to machine learning, deep learning can

1. simplify the pipelines from signal pre-processing, feature extraction to classification
2. end-to-end-learning: with the hierarchical structures of deep learning neural network, features of EEG data can be learned by the raw data or minimally preprocessed data without domain-specific processing and feature extraction.
3. be applied to multiple different classification tasks.
4. facilitate the development of generative modelling and domain adaptation. Generative modelling can be leveraged to learn intermediate representations or for data augmentation.

The combination of the deep neural networks and other techniques, such as correlation alignment, enables the end-to-end learning of domain-invariant representations and preserving task-dependent information. This can be applied to EEG processing.

The convolutional neural network (CNN) is one of the most popular types of deep learning and has been successfully developed to automate the detection of seizure, sleep disorder, and Parkinson's disease. CNN enables the algorithms to learn higher-level features through the training data without the need of human intervention. CNN tends to learn better as network get deeper which will affect the computational time(Oh *et al.*, 2018).

A typical CNN contains the convolution, max-pooling and fully-connected layers (Oh *et al.*, 2018; Acharya *et al.*, 2018; Faust *et al.*, 2018).

The convolutional layer convolves with the input signal with a kernel to extract the features. The result is known as the feature map which is the input for subsequent pooling layer.

The pooling layer performs down-sample on the output of the convolutional layer to reduce the dimension of data and prevent overfitting. The pooling operation can be average, sum or max. The most common operation of this layer is max-pooling. Max-pooling operation selects the maximum value in each feature map.

The fully-connected layer connects to all the activations in pooling layer and predicts the outcome The number of classes is determined by the total number of fully-connected neurons in this layer.

5-3. Example of Deep Learning in EEG Applications

There were several applications which employed deep learning networks to automate the detection of sleep pattern and seizures by time-series EEG.

5-3-1. SLEEPNET for detection of sleep pattern

Sleep disorders are a worldwide health problem. The most common technique to evaluate sleep disorder is polysomnogram (PSG) which record several physiological signals, including EEG, during the sleep. Patients' sleep patterns are based on the visual scoring of EEG. Manual scoring is a time-consuming and tedious process. Furthermore, the scoring might be subjective.

(Biswal *et al.*, 2017) proposed SLEEPNET (Sleep EEG neural network) which used a deep recurrent neural network for automated sleep-wake scoring/staging. To overcome the variance of time series EEG recorded by PSG, due to the age, gender, sleep disorder and medication. Instead of developing and training multiple algorithms dedicated to different groups, the authors developed and trained a signal algorithm based on a large dataset.

SLEEPNET system was composed of two modules, training and deployment modules.

The input of the training module is multi-channel EEG, and the output is the classified sleep stage sequence. The training module extracts features from the EEG data into 3 categories raw EEG features, spectrogram features and expert-defined features. To extract the time series EEG features, EEG recording was divided into 30-second epochs. EEG sampling rate was 200Hz and EEG recording channels was 6. For *ith* epoch,

1. Time-domain: The features of raw EEG were presented by the 3D matrix with dimension 6,000x6.

2. Spectrogram: Each 30-second epoch was further segmented into 29 sub-epoch of 2-second window length with 1-second overlap. Then perform Fast Fourier Transform to each sub-epoch to estimate the power spectrum density in 257 frequency bin between 0 to 100Hz which resulted in a feature matrix with the dimension 29 x 257.
3. Expert defined: Expert defined features are listed in table 4, 96 features in total.

Table 4: List of expert-defined features, 96 in total.

Domain	Feature	# of features
Time	Line length	6
	Kurtosis	6
Frequency	delta-total power ratio	12
	theta-total power ratio	12
	alpha-total power ratio	12
	delta-theta power ratio	12
	theta-alpha power ratio	12
	delta-alpha power ratio	12
	Kurtosis of delta band of spectrogram	3
	Kurtosis of theta band of spectrogram	3
	Kurtosis of alpha band of spectrogram	3
	Kurtosis of sigma band of spectrogram	3

Once the features of EEG data were extracted, the training module evaluated different classification methods, such as logistic regression, tree boosting, multilayer perceptrons and deep learning methods to find the best methods and the corresponding features. The evaluation process was done by splitting the dataset into training, validation, and test data. The best model was implemented in the deployment module. The result showed that the best model was the combination of deep learning recurrent neural network (RNN) and expert-defined features.

Based on the test data of 1,000 patients, SLEEPNET achieved 85.76% of classification accuracy compared to human-level annotation performance.

5-3-2. Detection seizure using EEG plot images

(Emami *et al.*, 2019) investigated the feasibility of automatic detection seizure by visual recognition using CNN. Instead of providing EEG data as input, the input of CNN was EEG plots which were used by EEG-ers to identify the seizures.

In their study, EEG time series data were epoched by different time parameters, 0.5, 1, 2, 5 and 10 seconds and converted to EEG plots with 224 x 224 pixels. EEG data were segmented by one second with the overlapped with previous epoch, except window <= 1 seconds. The classifier was trained and tested by 'leave-one-out', i.e. trained by 23 out of 24 subjects and the remaining subject for the test. The output of a given EEG plot was 'seizure' or 'non-seizure'. The result showed that EEG plot of 1 second yielded the highest true positive rate. 0.5 second was too short to identify seizure while 10 seconds were too long to detect the onset of the seizure.

The medium true positive rate was 74% which was higher than commercial seizure detection software, BESA (20%) and Persyst (31%). The median of detected seizure rate by minutes was 100% also higher than BESA (73.3%) and Persyst (81.7%). The false positive rate was 0.2 per hour. The authors also suggested that various datasets could improve the efficacy of CNN for seizure detection.

5-3-3. Seizure detection by raw EEG data in time and frequency domains

(Zhou *et al.*, 2018) demonstrated that deep learning models can be trained by raw EEG signals without prior features extraction. They also compared the performance using raw EEG data in the time domain and the frequency domain as the input of the neural network. Three classification tasks were tested, interictal vs. preictal and interictal vs. ictal and interictal vs. preictal vs. ictal. Two epileptic public databases were used, intracranial EEG Freiburg database and surface EEG CHB-MIT database.

When using the frequency domain signal, the average detection rates using were 96.7%, 95.4%, and 92.3% for three classification tasks for Freiburg datasets. For CHB-MIT datasets, the mean accuracies were 95.6%, 97.5%, and 93%.

When using raw EEG signal in the time domain, the average detection rates using were 91.1%, 83.8%, and 85.1% for three classification tasks for Freiburg datasets. For CHB-MIT datasets, the mean accuracies were 59.5%, 62.3%, and 47.9%

The authors suggested the reason that the accuracy was higher using Freiburg datasets than CHB-MIT datasets was because Freiburg datasets were intracranial EEG. In addition, unlike Freiburg datasets were recorded directly from focal areas, CHB-MIT datasets were recorded from whole-brain areas which might contain more redundant information. For the performance between using frequency and time-domain signals, the authors suggested that CNN might extract more effective features based on the frequency domain than the time domain.

6. Aim and Methodology of the present study

The aim of this study attempts to improve epilepsy management. This study is to develop a deep learning algorithm to automate the detection of epileptic activities and seizures using EEG. The developed system is hoped to help to make the clinical decision, find the optimal treatment plan, and improve the quality of life for epilepsy patients.

Figure 4 illustrates the epilepsy management and the areas where EEG can be applied to improve.

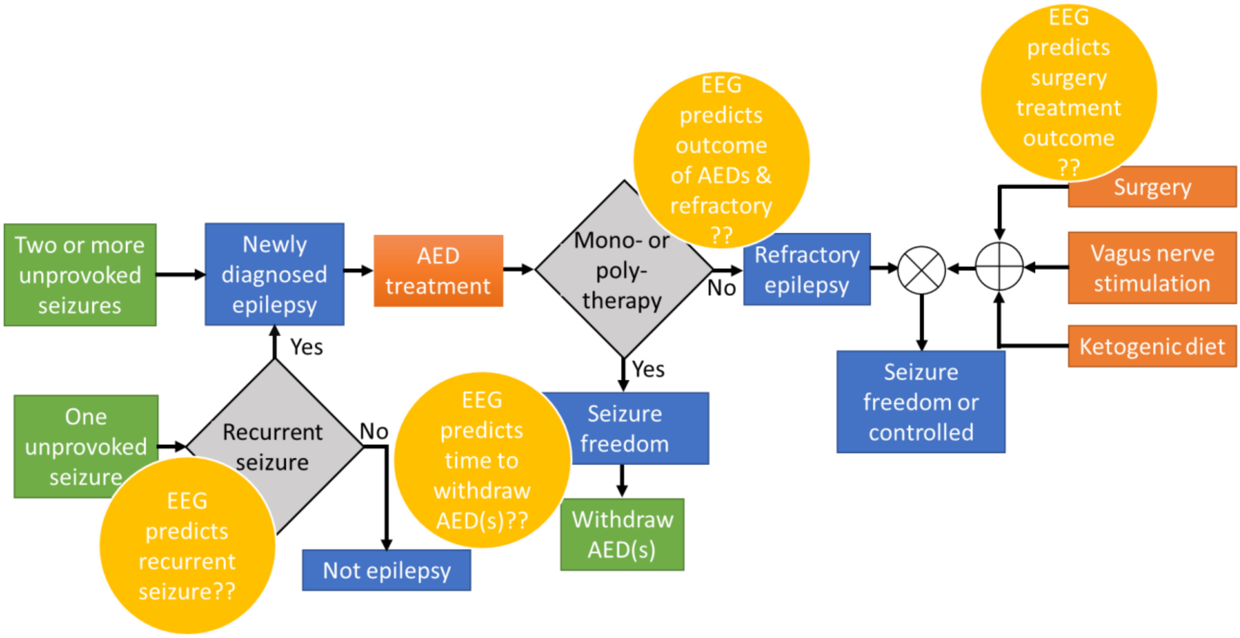


Figure 4: An illustration of epilepsy management and areas (circle parts) to be improved.

6-1. Ares of Epilepsy Management to be improved

As shown in Figure 4, the following areas in epilepsy management can be improved.

6-1-1. Predict the recurrent seizures

As mentioned in the introduction section, three conditions define epilepsy. The first and third conditions are clear. However, one unprovoked seizure presents a challenge in clinical practice.

6-1-2. Predict the response of the patients to AEDs

About 70% of patients can achieve seizure freedom through AEDs. However, some studies have shown that AEDs are one of the major parts of the direct cost. EEG might offer the clinicians a metric to determine the best and most suitable AED for the individual in terms of the lowest cost, best outcome, and minimal advert effect.

Refractory epilepsy remains a problem despite more AEDs available since the 1990s. Besides the surgery option, refractory epilepsy patients can continue AED treatment to reduce the number of seizures. EEG might be able to predict the response of the patients to the combination of multiple AEDs.

The following factors have demonstrated their effectiveness to predict if the epilepsy patients can achieve seizure remission within 5 years after their first clinical visit for epilepsy,

Age, gender, type of epilepsy, number of seizures before treatment, family epilepsy history, traumatic brain injury, frequency of seizure after last clinic visit, opinion of current treatment effectiveness from the clinician (Hughes *et al.*, 2018).

6-1-3. Predict the outcome of the surgery

About 30% of patients have refractory epilepsy. Surgery is an option for them. Depending on their epilepsy syndromes, seizure freedom with surgery treatment ranges from 30% to 80% of patients, (Strzelczyk *et al.*, 2008). EEG might be used to predict the outcome of surgical treatment.

Meanwhile, as mentioned earlier, surgery is more cost-effective than AED treatment. If EEG can predict the outcome of surgery treatment, it might encourage non-refractory epilepsy patients to opt for this option to reduce the economic burden.

6-1-4. Estimate the time of AEDs withdrawal

AEDs are the major contributor to epilepsy's direct cost. Therefore, it could be helpful to have an objective measurement for the outcome of epilepsy relapse after withdrawal or reduce the dose of AEDs to reduce the financial burden.

The role of EEG in estimating the time to withdraw AEDs remains uncertain(Smith, 2005).

6-2. Methodology

As shown in figure 4, there are 4 potential areas to be improved in epilepsy management. Each area has its challenges and problems. However, these difficulties might be related to brain abnormalities which can be characterised by the exhibited epileptic activities and seizures.

This study is to develop a deep neural network to automate the detection of epileptic activities and seizures using EEG. Figure 5 shows a typical feed-forward neural network which consists of three layers, input layer, hidden layer, and output layer.

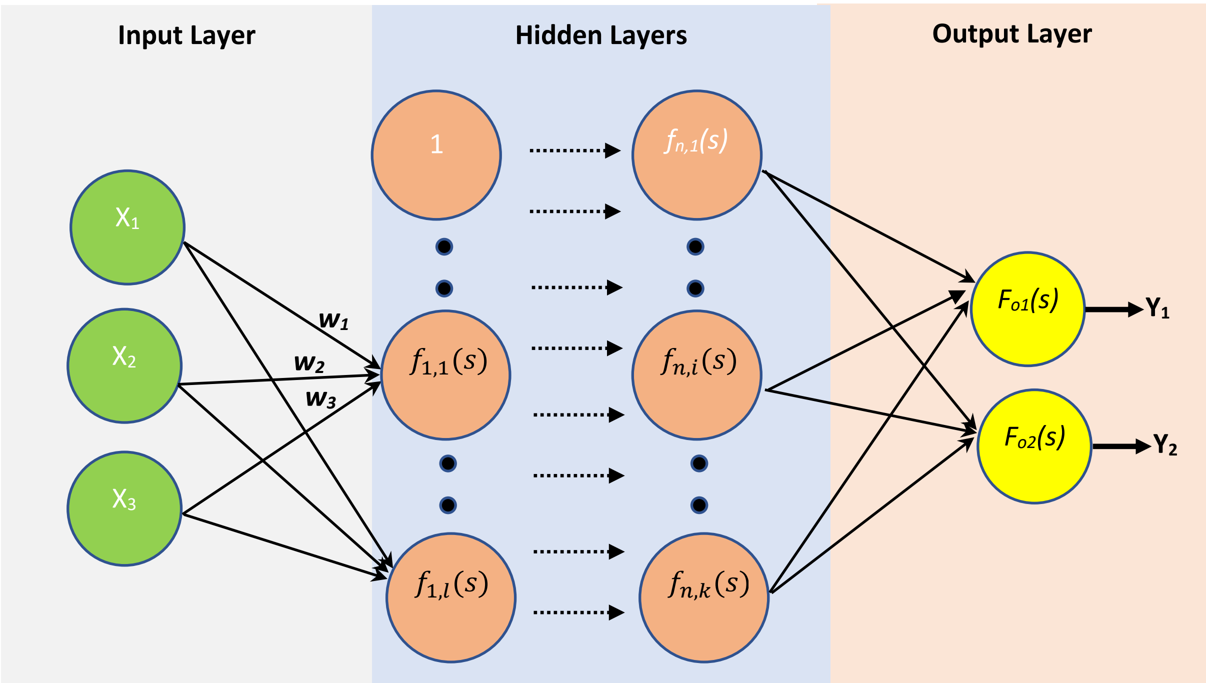


Figure 5: A typical feed-forward neural network architecture which consists of three layers, input layer, hidden layer, and output layer.

6-2-1. The architecture of deep neural network architecture

The network architecture has to be chosen, such as convolutional neural network, or recurrent neural network.

6-2-1-1. Input layer

The input of the neural network will be raw EEG data. EEG data will be segmented into epochs with selected window length. Other individual-specific features, such as age, gender etc, might be used for some classification problems.

6-2-1-2. Hidden layers

How many hidden layers are required?? "Deep" is normally referred to as the number of hidden layers.

6-2-1-3. Output layer

The output of the deep neural network will depend on the classification tasks (the areas to be improved). For example, to predict the withdraw AED after a substantial seizure-free period, the output could be, 'continue AED', 'taper AED' and 'withdraw AED'.

6-2-2. Implementation of deep neural network

This development can be implemented by MATLAB or Python. There are several machine learning open sources available for Python, such as SciKit-Learn, PyTorch, TensorFlow and Keras. If using Python, a suitable package will be chosen.

6-2-3. Data for training the deep neural network

The deep neural network requires large labelled data to train the algorithm. There are several open-source EEG databases which can be downloaded and used to evaluate the model,

1. CHB-MIT Scalp EEG Database(Shoeb, 2009), EEG data were acquired at the Children's Hospital Boston, from paediatric subjects with intractable seizures. Each recording of one subject contained 9 to 42 continuous EEG data files in edf format. The sampling rate was 256 Hz. https://physionet.org/content/chbmit/1.0.0/

2. EEG database of Epilepsy Centre, Bonn(Andrzejak *et al.*, 2001): It contains 5 datasets (A-E). EEG of sets A and B are surface EEG from 5 health subjects. Sets C, D and E were intracranial EEG. Sets C and D contained EEG recorded during seizure-free intervals. Set E contains records with seizure activity. The sampling rate of the data was 173.61 Hz. The file format was txt.

   http://epileptologie-bonn.de/cms/front_content.php?idcat=193&lang=3

3. TUH EEG Corpus (Harati *et al.*, 2014): TUH EEG resource is the world's largest publicly accessible EEG database. The database consisted of over 30,000 clinical EEG recordings at the Temple University Hospital from 2002 - present. The database included EEG of the following types of seizure, simple partial seizure, complex partial seizure, focal non-specific seizure, generalized non-specific seizure, absence seizure, tonic seizure, tonic-clonic seizure, and myoclonic seizure. The sampling rate was 250Hz. Registration is required to download the data. https://www.isip.piconepress.com/projects/tuh_eeg/html/downloads.shtml

4. The SWEC-ETHZ iEEG Database(Burrello *et al.*, 2019). Data were saved in the format of mat (native MATLAB). The long-term database was recorded from 18 patients. Each file contained a one-hour recording of a specific patient. The sampling frequency of the long-term database was 512 or 1024Hz. The short-term database contained seizure EEG from16 patients. Each file contained EEG data 3 minutes before seizure onset, ictal EEG, and 3 minutes after seizure offset. The sampling frequency of short-term dataset was 512Hz. http://ieeg-swez.ethz.ch/

5. Freiburg database (Winterhalder *et al.*, 2003): It is not free to download anymore but data can be purchased.

http://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database or http://epilepsy-database.eu/

6-2-4. Evaluation of deep neural network

The performance of the built neural network will be assessed by overall accuracy, sensitivity, speciality and F score. These metrics are defined by the following equations.

Overall Accuracy (acc)
$$acc = \frac{TP + TN}{P + N} \tag{5}$$

Sensitivity (sen)
$$sen = \frac{TP}{TP + FN} \tag{6}$$

Speciality (sep)
$$sep = \frac{TN}{TN + FP} \tag{7}$$

F Score (F_{SCORE})
$$F_{SCORE} = 2 \times \frac{sen * sep}{sen + sep} \tag{8}$$

where *TP*: true positives, *TN*: true negatives, *P*: positives samples, *N*: negatives samples, *FN*: false negatives, *FP*: false positives.

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