First seizure clinics in the evaluation and management of first seizures

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List of abbreviations

This list includes all abbreviations used more than once in the body text.

AD	Alzheimer's disease
aIRR	adjusted incidence rate ratio
aOR	adjusted odds ratio
ASM	antiseizure medication
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CT	computerised tomography
DLB	dementia with Lewy bodies
ED	emergency department
EEG	electroencephalogram
FSC	first seizure clinic
FTD	frontotemporal dementia
GCS	Glasgow coma scale
GP	general practitioner
HR	hazard ratio
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
IHD	ischaemic heart disease
ILAE	International League Against Epilepsy
MRI	magnetic resonance imaging
OR	odds ratio
PWE	people with epilepsy
QALY	quality-adjusted life year
QoL	quality of life
SD	standard deviation
SIR	standardised incidence ratio
SMR	standardised morbidity ratio
TBI	traumatic brain injury
VAED	Victorian Admitted Episodes Dataset
VEMD	Victorian Emergency Minimum Dataset

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Declaration

I declare that the work presented here is my own work and contains no material previously published or written by another person, except where due reference has been made in the text.

The material has not previously submitted for the award of any other degree or diploma.

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Literature review

1. Introduction

Seizures are a common presentation in clinical neurology, with approximately 1 in 10 people having experienced at least 1 seizure over the course of their life.[1] Seizures account for 1–2% of emergency department (ED) presentations, and nearly one quarter of those are first seizure presentations.[2]

The evaluation and management of first seizures is of critical importance in delivering optimal patient care and improving long-term outcomes. However, despite recent advances, and promising preliminary results for the role of first seizure clinics (FSCs), there remains a paucity of evidence surrounding the use and effectiveness of FSCs, and their strengths and potential limitations.

Further research in this area would be of benefit from clinical and health service management perspectives to quantify the role of FSCs, optimise their use, and thereby ensure the best patient outcomes.

2. Clinical background and definitions

A seizure is defined by the International League Against Epilepsy (ILAE) as a “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”.[3]

Seizures may be classified according to clinical features into 3 types[4]:

- *focal onset*, arising in one brain hemisphere, further sub-classified as:
    - *aware* or *impaired awareness*
    - *motor onset* (e.g. automatisms) or *non-motor onset* (e.g. autonomic, emotional or sensory seizures)
    - with possible progression to *focal to bilateral tonic–clonic* seizures
- *generalised onset*, originating within and rapidly engaging bilateral networks, which may be further divided into *motor* (e.g. tonic–clonic) and *non-motor* (absence seizures)
- *unknown onset*

Figure 1 shows a more detailed sub-classification of each type.

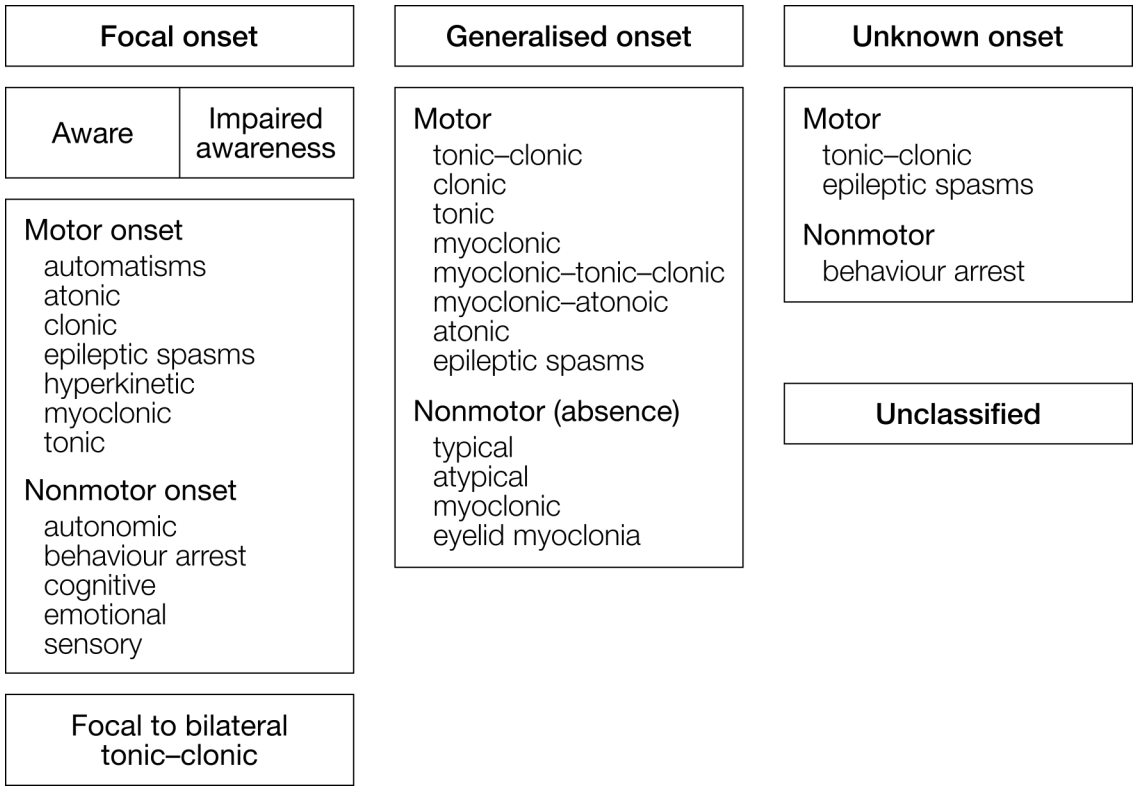

Figure 1. Classification of seizures according to clinical features

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Of these 3 types, focal seizures are the most common type in adults, and focal impaired awareness seizures are the most common form of focal seizure.[5]

By way of illustration, examples of focal seizure presentations may include[6]:

- abnormal muscle contractions, movements or vocalisations
- seeing flashing lights or other visual changes
- sensations of numbness, tingling, burning, cold or pain
- disrupted spatial perception or language ability
- feelings of fear, other emotions or a sense of déjà vu
- repetitive stereotyped movements (*automatisms*)

Examples of generalised seizure presentations include[7]:

- *absence* seizures, typically involving interruption of activity, blank stare and unresponsiveness to speech

- *generalised tonic–clonic* seizures, typically involving sustained bilateral symmetric muscle contraction (*tonic* phase), repetitive jerking (*clonic* phase), autonomic phenomena and loss of awareness
- *myoclonic* seizures, involving sudden, brief (<100 millisecond) muscle contractions
- *atonic* seizures, involving sudden loss of or reduction in muscle tone

Seizures may also be classified according to aetiology as:

- *acute symptomatic* (or *provoked*) seizures,[8,9] which occur contemporaneously with a systemic insult (e.g. toxins, medications or metabolic derangement) or brain insult (e.g. stroke, traumatic brain injury [TBI] or central nervous system [CNS] infection)[9,10]
- *reflex* seizures, which occur in some epilepsy syndromes and are evoked by specific afferent stimuli or activities[11]
- *unprovoked* seizures, further divided[5,12] into:
    - *remote symptomatic* and *progressive symptomatic* seizures, which occur in relation to pre-existing static (remote) or progressive brain injury[5,10,12] (e.g. previous TBI, Creutzfeldt–Jakob disease or age-related degeneration[9])
    - unprovoked seizures associated with specific *epilepsy syndromes*[10] (e.g. Dravet syndrome[13])
    - unprovoked seizures of unknown aetiology[10,12] (*idiopathic* or *cryptogenic* seizures[5])

Note that, unlike acute symptomatic seizures, both unprovoked and reflex seizures are not associated with transient pathology. Further assessment of unprovoked/reflex seizures may accordingly lead to a diagnosis of *epilepsy*, which has been conceptualised by ILAE as a "disorder of the brain characterised by an enduring predisposition to generate epileptic seizures".[3] More specifically, since the latest revision in 2014,[8] epilepsy is considered by ILAE to be defined by any of:

- 2 or more unprovoked/reflex seizures more than 24 hours apart
- 1 unprovoked/reflex seizure, with factors increasing the probability of recurrence over 10 years to the level generally seen after 2 unprovoked seizures (at least 60%)
- diagnosis of an epilepsy syndrome

Despite the overlap in the diagnostic categories of seizure and epilepsy, less than half of patients with a first seizure will go on to have epilepsy.[12] However, in a patient whose first seizure might indeed be a manifestation of epilepsy, treatment decisions might need to be made weighing the risk of recurrence, evaluating the commencement of antiseizure medications (ASMs) and

balancing their potential toxicity.[10,14] The initial evaluation of and approach to first seizures, then, is of critical importance in providing adequate care and guiding optimal management.[10,15]

3. Initial assessment and management of first seizures

The initial assessment and management of first seizures are complex endeavours. This section describes typical aspects of those processes, which generally occur across multiple settings – acutely in the ED, followed by neurologist referral for further assessment and management in a hospital outpatient or community setting.

Acute assessment

Most patients with first seizures, particularly for convulsive seizures, present to hospital EDs, though patients with nonconvulsive epileptic symptoms may instead initially present to general practitioners (GPs).[16]

In the acute setting, following the emergency management of any acute compromise to airway, breathing or circulation,[16] the initial history focuses on[6]:

- characterising the event as a true epileptic seizure and ruling out other diagnoses (such as syncope, migraine or psychogenic nonepileptic seizure)
- establishing whether any similar events have previously occurred
- evaluating past history, family history and medications for seizure precipitants or risk factors

If the event is indeed characterised as an epileptic seizure, other history, examinations and investigations aim to assess for other injuries associated with the seizure, and ascertain whether there is an acute symptomatic cause which must be immediately managed (such as CNS infection, trauma, toxins or metabolic derangement, as described in section 2).[6,16]

Table 1 shows a representative range of common investigations which might be performed in this acute setting.

Table 1. Possible initial investigations in first seizures[14,16]

Investigation	Possible acute symptomatic findings
Full blood examination (FBE)	Evidence of infection
Blood glucose Urea, electrolytes and creatinine (UEC) Calcium, magnesium and phosphate (CMP)	Hypoglycaemia Other metabolic abnormalities
Blood gases	Severe acid–base disturbances Hypoxia or respiratory failure
Liver function tests (LFTs)	Liver failure Derangement due to alcohol toxicity
Blood alcohol Urine drug screen	Drug intoxication or withdrawal
Electrocardiogram (ECG)	Cardiogenic cause of hypoxic seizure or collapse
Computerised tomography (CT) of the brain	Ischaemic stroke or haemorrhage Traumatic brain injury

Once any conditions requiring urgent management have been excluded, patients are typically referred to hospital outpatient or community neurologists for further assessment.[14,17]

Further outpatient/community assessment

Guidelines recommend that first seizure patients should be reviewed by a neurologist within 2 weeks.[14,18] For a patient with an apparent unprovoked first seizure, this assessment focuses on confirming that characterisation, investigating for any other acute or remote symptomatic causes or epilepsy syndromes, and determining whether to treat with ASMs.[15,17]

Particular focus in the history should be placed on determining whether there may have been any previous epileptic events before the supposed “first” seizure. A retrospective review by Firkin et al. of 220 patients referred for “first seizure” assessment demonstrated that 41% (n = 90) had had at least 1 previous event.[19] As described in the previous section, 2 or more unprovoked (or reflex) seizures at least 24 hours apart would be consistent with a diagnosis of epilepsy.

If not performed in the acute setting, a routine electroencephalogram (EEG) may be performed to noninvasively characterise potentially epileptiform brain activity.[6,14] The assessment is complicated, however, by the fact that a normal EEG does not rule out the presence of epilepsy, and, conversely, many abnormal EEG findings are nonspecific.[6] If the routine EEG is uninformative, guidelines recommend performing a subsequent sleep-deprived and/or prolonged EEG.[14]

Guidelines also recommend obtaining magnetic resonance imaging (MRI) of the brain,[14] which is more sensitive than CT for detecting a number of epileptogenic structural abnormalities, including smaller infarcts or tumours, as well as mesial temporal sclerosis and cortical dysplasia.[6,16]

The assessment may be completed at the first appointment, or may span 2 or 3 appointments,[20] and culminates in confirming the occurrence of a seizure, and identifying the seizure type, aetiology and any comorbidities.[15] If the assessment reveals a history of more than 1 unprovoked seizure, or the ILAE criteria are otherwise met, the diagnosis of epilepsy is made, and the epilepsy type and (if applicable) epilepsy syndrome are identified.[15,20]

Initial management

The diagnosis resulting from the assessment process, and an evaluation of the future risk of seizures, subsequently inform patient management, combined with weighing individual patient factors, comorbidities and preferences.

Education and lifestyle advice. Following a diagnosis of a first unprovoked seizure, guidelines recommend that patients, and their families or carers, should receive education on topics such as the nature and cause of seizures, management options, and risks associated with seizure recurrence and epilepsy.[14,15] Lifestyle advice should be provided around safety and risk management (including restrictions on driving and avoidance of other risky activities), avoidance of possible triggers, and seizure first aid.[14,15]

The occurrence of a seizure may have implications for a patient's ability to drive. In Australia, no person who has experienced a seizure is fit to hold an unconditional driving licence.[21] After a first-ever seizure, a private driver may be granted a conditional licence after 6 months without seizures (5 years for a commercial driver).[21] In other cases, unless an exception applies, a conditional licence may be granted after 12 months for a private driver (10 years for a commercial driver).[21]

Commencement of ASMs. ASMs are available for use to reduce the risk of seizure recurrence; however, their use following a first unprovoked seizure remains controversial and should be individualised.[17] In a meta-analysis by Krumholz et al. of 5 studies involving 1,600 patients, immediate treatment with ASMs resulted in an absolute risk reduction of 35% (95% confidence interval [CI]: 23%–46%) in seizure recurrence over 2 years, compared with deferring treatment until after a second seizure.[12] However, rates of sustained long-term seizure freedom did not vary between immediate (88%) or deferred (87%) treatment with ASMs.[12]

At the same time, ASMs are not without their own side effects. In the Krumholz et al. review, adverse effects were reported in 22% (*n* = 246/1126) of the patients treated with ASMs.[12] All reported adverse effects appeared to be mild,[12] and included mood deterioration, dizziness and

unsteadiness, nausea and vomiting, drowsiness, and poor memory and concentration.[22] Adverse effects appeared to be reversible on discontinuation of the responsible drug.[12]

A more recent study by Bao et al. attempted to combine such observations on seizure recurrence and ASM side effects, using Markov decision modelling to simulate a clinical trial comparing overall quality of life (QoL) under immediate and deferred treatment.[23] Bao et al. found that immediate treatment maximised expected quality-adjusted life years (QALYs) – resulting, in one case, in 19.04 QALYs with immediate treatment, compared with 18.65 QALYs for deferred treatment, a difference in QoL worth an estimated US$19,500 per person.[23] However, the results of the model are limited by reliance on estimates from previous unrelated studies, and such findings have yet to be reproduced in actual clinical trials.

Translated into clinical practice, the decision whether to commence ASMs after a first seizure is a balance taking into account each individual patient's factors which may increase the risk of seizure recurrence. These factors include focal onset of seizures, epileptiform EEG abnormalities, previous TBI, nocturnal seizures, and abnormalities on neurological examination or neuroimaging.[12,24] At present, the Australian *Therapeutic Guidelines* recommend that deferring pharmacotherapy until after a second seizure is reasonable, unless the recurrence risk is high or the patient prefers to be treated immediately.[24] Overall, in a study by Sharma et al. of 184 Western Australian patients with a single seizure at diagnosis, 147 were recommended ASMs following neurologist assessment, of whom 112 accepted the recommendation and commenced treatment.[25]

Selection of ASMs. If it is decided to commence pharmacotherapy with ASMs, a number of drugs are available for this indication, shown in Table 2.

Table 2. Antiseizure medications available in Australia

Seizure classification	First-line ASM	Second-line ASMs
Focal seizures	Carbamazepine	Clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, phenobarbital, phenytoin, pregabalin, sodium valproate, tiagabine, topiramate, zonisamide
Generalised tonic–clonic seizures	Sodium valproate	Carbamazepine, clobazam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate
Absence seizures	Ethosuximide, sodium valproate	Clobazam, clonazepam, lamotrigine
Myoclonic seizures	Sodium valproate	Clobazam, clonazepam, levetiracetam, phenobarbital
Infantile spasms	Prednisolone, tetracosactide	Clonazepam, sodium valproate, vigabatrin
Other ASMs		*Acetazolamide, brivaracetam, diazepam, midazolam, perampanel, primidone, rufinamide, stiripentol, sulthiame*

Adapted from the Australian Medicines Handbook[26]

In Australia, the *Therapeutic Guidelines* recommend carbamazepine as a first-line ASM in seizures with focal onset, and sodium valproate in seizures with generalised (or unclear) onset.[24] However, these recommendations generally have limited evidentiary support – many head-to-head trials have been conducted, but it is rare to demonstrate one ASM is more or less effective than another on the whole.[27] For example, Table 3 summarises the findings of several recent systematic reviews comparing different ASMs – overwhelmingly, most ASMs are found to have similar efficacy.[28–31]

Table 3. Selected recent systematic reviews comparing antiseizure medication efficacy

Study	Seizure type	Findings
Nevitt et al.[28] (Cochrane review)	Focal seizures	Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbitone, phenytoin, sodium valproate, topiramate and zonisamide all have similar efficacy, measured by time to 12-month remission. Levetiracetam, the only exception, was shown to be inferior to carbamazepine and oxcarbazepine only.
Nevitt et al.[28] (Cochrane review)	Generalised seizures	Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbitone, phenytoin, sodium valproate and topiramate all have similar efficacy, measured by time to 12-month remission.
Lattanzi et al.[29]	Focal seizures	Controlled-release carbamazepine, eslicarbazepine (active metabolite of oxcarbazepine[30]), lacosamide, levetiracetam and zonisamide and all have similar efficacy, measured by 12-month seizure freedom, and similar adverse effect profiles.
Campos et al.[31]	Focal seizures	Carbamazepine, clobazam, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, sulthiame and topiramate all have similar efficacy, measured by seizure freedom at the end of maintenance treatment.

The selection of ASM is therefore a complex question of individual patient characteristics, drug tolerability for each individual patient, and confounding factors.[27]

In particular, for females of childbearing potential, many ASMs, such as sodium valproate, are highly associated with major fetal malformations. Some, such as phenobarbitone, phenytoin and carbamazepine, can additionally interfere with the efficacy of oral contraceptives through induction of the cytochrome P450 enzyme system.[32,33] Particular care is therefore required when selecting ASMs in these patients. For example, the *Therapeutic Guidelines* recommend levetiracetam over sodium valproate in females of childbearing potential without reliable contraception.[24]

Management of comorbidities. As will be discussed in the next section in greater detail, numerous medical conditions are associated with seizures. The assessment and management of seizures, then, naturally involves an appreciation of these comorbidities.[15] For example, remote symptomatic seizures may be associated with past strokes,[34] and so the holistic management of a first seizure patient with such a history should include management of vascular health. As a further example, first seizures are commonly associated with distress and psychological effects, with consequential or concomitant mood deterioration or depression.[35,36] The approach to first seizures, then, should include screening for such conditions, and offering appropriate support and referrals.[15]

4. Associated conditions, risk factors and comorbidities

As described in the previous section, the assessment and management of first seizures require an appreciation of the range of conditions associated with seizures. Some conditions are directly connected to the aetiological classification of seizures described in section 2, whereas others appear more loosely connected as risk factors and common comorbidities. In yet other cases, the relationship is unclear, and emerging evidence is currently shaping our evolving understanding. In each case, understanding these relationships is important in delivering holistic care for patients with seizures, and so they are presented together in this section.

Acute symptomatic seizures

Acute symptomatic seizures are those which occur in close association with a systemic or documented brain insult. They are not considered unprovoked seizures, and so do not contribute to a diagnosis of underlying epilepsy.

The ILAE consensus definition of acute symptomatic seizures arises from a systematic literature review and discussion presented by Beghi et al.,[9] which describes a number of conditions that acute symptomatic seizures may occur in association with:

- cerebrovascular disease, including stroke,[34] intracranial haemorrhage and arteriovenous malformation[9]
- TBI,[37–39] including intracranial surgery or subdural haematoma[9]
- anoxic encephalopathy[9,40]
- presentation or relapse of multiple sclerosis, or other autoimmune diseases[9]
- encephalitis, meningitis,[41] and other CNS infections, such as neurocysticercosis, cerebral tuberculoma or brain abscesses[9] (but see the next subsection for congenital toxoplasmosis or Creutzfeldt–Jakob disease)
- a range of metabolic disturbances, including hypoglycaemia, hyperglycaemia with ketoacidosis, hyponatraemia, hypocalcaemia, hypomagnesaemia, uraemia and elevated creatinine[9]
- febrile illness, particularly in children[9,24]
- other infections associated with fever, acute illness or severe metabolic disturbance, including malaria and HIV[9]
- alcohol withdrawal or intoxication[9,42,43]
- withdrawal of drugs, particularly barbiturates or benzodiazepines; or intoxication with recreational drugs, including cocaine, stimulants, hallucinogens and inhalants[9]

In general, seizures occurring within 7 days of such acute insults are considered acute symptomatic.[9]

Table 4 in Appendix 1 summarises a list of *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* (ICD-10-AM) codes of acute symptomatic causes of seizures described in this subsection.

Remote symptomatic seizures

Seizures that occur in association with static brain injury, beyond the acute insult, are considered remote symptomatic:

Stroke. Seizures occurring more than 7 days after a stroke are considered remote symptomatic seizures.[9] In a systematic review by Wang et al. of 18 studies and 14,724 stroke patients, 4.5% of patients experienced 1 or more such seizures, and the overall incidence rate was 18 (95% CI: 15–22) per 1000 person-years.[34]

In a representative study by Bladin et al. of 1,897 stroke patients, cortical location of infarct and stroke disability were the only factors associated with increased risk of a post-stroke seizure, but neither was associated with recurrent seizures in the long term.[44] Similar results have been reported by Leung et al.[45] and Berges et al.[46]

Traumatic brain injury. Seizures occurring >7 days after TBI are considered remote symptomatic.[9] In a study by Annegers et al. of 4,541 patients with TBI, the 30-year cumulative incidence of subsequent seizures was 2.1% for mild TBI, 4.2% for moderate TBI and 16.7% for severe TBI, with an overall standardised incidence ratio (SIR) of 3.1 (95% CI: 2.5–3.8).[37] Similar results have been reported more recently by Wang et al., who followed 3,093 TBI patients and found 6.6% (*n* = 196/2987) of those without acute symptomatic seizures later developed remote symptomatic seizures over 2 years.[39]

Both Annegers et al. and Wang et al. also identified that brain contusion, linear skull fracture and impaired consciousness (respectively measured by extended loss of consciousness or amnesia, and initial Glasgow coma scale [GCS] score) were associated with greater risk of remote symptomatic seizures.[37,39]

Encephalitis. Seizures occurring >7 days after CNS infection are considered remote symptomatic.[9] In a study by Zelano et al. of 2,573 patients with encephalitis, 211 (8.2%) went on to develop epilepsy (with remote symptomatic seizures).[47] The risk was greatest in the 443 patients with herpes simplex viral encephalitis (hazard ratio [HR] 14.23, 95% CI: 9.37–21.61).[47] The occurrence of acute symptomatic seizures and admission requiring mechanical ventilation were independent risk factors for epilepsy.[47]

Other CNS infections. Bacterial meningitis is also associated with remote symptomatic seizures, though at a lower rate than encephalitis.[41,47] In the Zelano et al. study, of 2,812 patients with bacterial meningitis, 118 (4.2%) went on to develop epilepsy (HR 2.69, 95% CI: 2.11–3.43).[47] Other CNS infections with long-term chronicity, such as congenital toxoplasmosis and Creutzfeldt–Jakob disease, are also associated with remote symptomatic seizures.[9]

Neurodegenerative disease and progressive symptomatic seizures

Seizures may also occur in association with progressive neurodegenerative disease, known as progressive symptomatic seizures.[5,9]

In a study by Beagle et al. of 1,846 patients with neurodegenerative disease, the cumulative probability of developing seizures was highest in Alzheimer's disease (AD) (13.4%) and dementia with Lewy bodies (DLB) (14.7%), and lowest in frontotemporal dementia (FTD) (3.0%).[48] Similarly, in a review by Sarkis et al. of 77 patients with progressive symptomatic seizures due to dementia, the pathologies noted were AD (88%), vascular dementia (6%), DLB (5%), FTD (4%) and nonfluent primary progressive aphasia (1%) (sum exceeds 100% due to mixed pathologies).[49]

In such patients with dementia, it is estimated that the incidence of seizures is 5–10 times higher than in the general population.[50,51] In a clinical setting, the implication is that a first unprovoked seizure may herald the onset of neurodegenerative disease, prompting consideration of further investigation and follow-up.[15]

Evidence also suggests that, in these patients, the prognosis of seizures and neurodegenerative disease are inter-related, such that in a retrospective observational study of 35 patients with early AD, Vossel et al. found that cognitive decline occurred earlier in patients with epilepsy or subclinical epileptiform activity, compared to those without.[52]

Despite these observations, firm information on the association between seizures and dementia is lacking, with a 2017 systematic review by Subota et al. concluding that there are “significant gaps” in the literature in this area.[53] While studies tend to agree that focal impaired awareness seizures are most common in this population,[51,52,54,49] conflicting results have been reported on whether convulsive[54] or non-convulsive[52] presentations predominate.

The aetiological relationship between neurodegenerative disease and seizures is also unclear; indeed, it is unclear whether the two arise independently from a common pathway, or whether the mechanisms are interdependent.[15] Various mechanisms have been proposed,[55] including mesial temporal lobe neuronal loss and gliosis,[51] presenilin-1 mutations and associated β-amyloid abnormalities,[56,57] and seizure-related temporal lobe damage.[53]

To summarise, Table 5 in Appendix 1 shows a list of ICD-10-AM codes of remote and progressive symptomatic causes of seizures. Note that, as described in section 2, remote or progressive symptomatic seizures are considered “unprovoked”, and may contribute to a diagnosis of epilepsy.

Other medical comorbidities

A number of other medical conditions, though not directly aetiologically related, are also associated with seizures:

Ischaemic heart disease. Given that cerebrovascular disease may contribute to seizures through acute and remote symptomatic aetiologies, it is unsurprising that other vascular diseases display association. For example, in a study of 7,461 patients with newly diagnosed epilepsy compared with age-sex-matched controls, Chen et al. report an SIR of 4.18 (95% CI: 3.54–4.91) for ischaemic heart disease (IHD).[58]

Cancer. Perhaps more surprisingly, Chen et al. also report that those with epilepsy had higher risk of developing cancer than controls (SIR 1.97, 95% CI: 1.56–2.46), including both CNS and non-CNS cancers.[58] Whether increased cancer risk is due to aetiological connection with epilepsy, an adverse effect of ASMs or a product of confounding by surveillance bias has been the subject of debate.[58,59] However, in a study by Kaae et al. controlling for increased surveillance post initial epilepsy diagnosis, epilepsy was associated with increased CNS, mouth, throat and respiratory tract cancers independent of ASM use.[60] These results suggest there may be pathogenic factors common to epilepsy and cancer.[58]

Migraine and other paroxysmal “seizure mimics”. Other medical conditions share clinical features with epilepsy, and have traditionally been regarded only as distinct entities which may mimic seizures. However, some conditions – such as migraine, vertigo, parasomnias and rare paroxysmal dyskinesias – are known to share molecular and genetic features with epilepsy, and may be more closely related than previously thought.[61] In particular, migraine is 2.4 times as common in people with epilepsy (PWE) than those without epilepsy.[61,62] Comorbid “migralepsy” exists in a number of clinical syndromes, and mutations in 3 genes known to cause familial hemiplegic migraine (*CACNA1A*, *ATP1A2* and *SCN1A*) also have epileptogenic potential.[61] Further research is required to assess these associations.

Psychiatric illness

Mounting evidence points to a close association between seizures and psychiatric illness:

Mood disorders in epilepsy. Bidirectional relationships between mental health and chronic disease are well-described, with increasing chronic morbidity associated with higher risk of depression,[63] and patients with depression more likely to develop chronic diseases.[64] The position is comparable in PWE,[65] with a systematic review by Fiest et al. reporting an overall prevalence of

active depression of 23.1% (95% CI: 20.6%–28.3%) among 29,891 PWE, and an odds ratio (OR) of 2.20 (95% CI: 1.07–4.51) for lifetime depression in PWE.[66]

Mood disorders in first seizure. In terms of first seizure patients, evidence suggests psychiatric illness may be present from first seizure onset. In a case–control study of 57 first seizure patients, Lane et al. report a higher prevalence of depression in unprovoked first seizure patients (33%) compared with controls (6%), with an OR of 7.25 (95% CI: 1.56–33.65).[35] Similarly, in an observational study of 85 patients by Velissaris et al., 52% described mood deterioration at 1 month from first seizure,[36] and 16% followed a trajectory of high-level depression and anxiety through to 12 months.[67] In first seizure patients aged 65 and older, depression and anxiety are the most commonly observed comorbidities (32.5% and 23.1%, respectively).[68]

Mood disorders as risk factors for seizure. Emerging evidence also suggests that psychiatric illness may even be an independent risk factor preceding seizure onset. In a retrospective review of administrative data of patients aged 65 and older, Martin et al. report that new-onset epilepsy was associated with preexisting mood disorders. In particular, the highest risk was found in patients with bipolar disorder (adjusted odds ratio [aOR] 1.96, 95% CI: 1.15–3.34), but association was also seen with unipolar major depressive disorder (aOR 1.45, 95% CI: 1.33–1.59).[69]

Psychotic disorders as risk factors. The Martin et al. study also found that new-onset epilepsy was significantly associated with psychotic disorders; namely, schizophrenia (aOR 1.65, 95% CI: 1.31–2.08) and psychosis not otherwise classified (aOR 2.30, 95% CI: 2.06–2.56).[69]

Other psychiatric conditions. Martin et al. also report that substance use disorders were an independent risk for new-onset epilepsy (aOR 2.50, 95% CI: 2.11–2.95).[69] Epilepsy was also significantly more common in patients with adjustment disorder and post-traumatic stress disorder ($p \leq 0.0001$), but the difference in risk was not significant when adjusted for confounding.[69]

In terms of these psychiatric risk factors for seizures, similar studies had previously reported comparable results in more limited populations.[70,71] What remains to be shown is whether these findings are reproducible prospectively, and in more general populations.

To summarise, Table 6 in Appendix 1 shows ICD-10-AM codes of medical and psychiatric conditions (other than symptomatic aetiologies) associated with seizures described in the preceding 2 subsections.

5. Outcomes and health burden of seizures and epilepsy

The importance of the assessment and management of seizures, and associated conditions, is underscored by the short- and long-term outcomes faced by patients, both from an initial first seizure, and from the consequences of epilepsy, if it is present.

Outcomes of first seizures

Social and emotional impact. The experience of a first seizure may have profound social and emotional consequences for patients.[72] As described in the previous section, Velissaris et al. found significant numbers of patients experienced mood deterioration or depression in the year after a first seizure.[36,67] Psychological factors driving this effect included: immediate emotional impacts (such as shock, fear and confusion), uncertainty around whether or when a seizure could recur, feeling loss of control over one's body, and increased awareness of one's vulnerability and mortality.[36]

Patients in the Velissaris et al. study also described significant social impacts arising from the seizure. More than half (58%) of patients described frustration due to driving restrictions impacting daily activities[36] – as described in section 3, Australian first seizure patients are generally subject to at least a 6-month non-driving period. Patients also described adverse effects of the seizure on their ability to fulfil family duties, undertake work responsibilities and engage in leisure activities.[36]

Long-term prognosis. In the longer term, a first seizure may have ongoing implications for patient outcomes if representing underlying epilepsy. Based on a systematic review by Krumholz et al., the long-term (>5 year) risk of seizure recurrence after an unprovoked first seizure, which might then lead to a diagnosis of epilepsy, is between 39% and 58%, with a point estimate of just under 50%.[12] The risk is by far the greatest in the first 1–2 years following the seizure, with a 21%–45% risk of recurrence within the first 2 years.[12]

Health burden of epilepsy

In the long term, epilepsy is associated with significant health burden. This burden predominantly arises from lost QoL due to the symptoms of epilepsy and associated disruption to day-to-day activities – for example, impacts on driving.[73] This morbidity is compounded by conditions attributable to seizures and epilepsy, such as the medical (e.g. IHD, cancer) and psychiatric (e.g. depression, anxiety) associations described in section 4, and injuries caused by seizures (e.g. fractures).[73]

In addition to this morbidity and associated mortality, epilepsy is associated with financial costs to society, primarily through lost productivity of PWE and their carers (such as “absenteeism” due to time taken off work, and premature exit from the workforce), and the cost of providing healthcare and welfare services.[73]

A 2020 Deloitte Access Economics report commissioned by Epilepsy Australia estimates the annual cost of epilepsy in Australia at $12.3 billion.[73] This is composed of lost wellbeing (non-financial costs) valued at $8.2 billion, and financial costs of $4.2 billion, the largest financial cost being lost productivity ($2.3 billion).[73] Over the working lifetime of PWE, Foster et al. describe life

table modelling estimating a loss of Australian gross domestic product alone of $32.4 billion, with a further $4.1 billion in excess direct healthcare costs, and over 14,000 excess deaths.[74]

It is clear, then, that seizures and epilepsy, particularly undertreated or uncontrolled epilepsy, can have significant impacts on patients and society. This highlights the importance of accurately assessing and effectively managing these conditions, to minimise this impact.

6. Importance of early intervention and the “treatment gap”

Nature of the treatment gap

Early and effective intervention has long been known to be an important determinant of favourable outcomes in seizure and epilepsy. One measure of this is the “treatment gap”, defined as the proportion of PWE who require, but do not receive, treatment.[75] The treatment gap is traditionally regarded as an issue primarily of low- and middle-income countries: a systematic review by Meyer et al. reports gaps exceeding 75% in low-income countries and 50% in most lower-middle and upper-middle-income countries, compared with gaps generally less than 10% in high-income countries.[75]

However, recent Australian data suggests that the treatment gap may be larger in our high-income healthcare system than previously believed. A study by Sharma et al. of 610 patients with newly diagnosed epilepsy found that only 427 (70.0%) commenced treatment at diagnosis.[25] A further 112 (18.4%) commenced treatment during follow-up, overwhelmingly due to experiencing further seizures, leaving 71 (11.6%) untreated at last follow-up (median follow-up 5.0 years).[25]

It is not strictly possible to conclude that these proportions entirely represent undertreatment per se – as described in section 3, the literature and guidelines do support deferring treatment in some circumstances. However, that the majority of patients who were initially untreated later commenced ASMs due to further seizures suggests that at least some of this proportion may represent a “treatment gap” to be closed.

Impact of diagnostic delay, underdiagnosis and undertreatment

One potential component of this “treatment gap” may be the effect of underdiagnosis and diagnostic delay – the time difference between first symptoms and first presentation for neurological assessment.

A study by Gasparini et al. examined the effects of diagnostic delay on long-term seizure freedom, over a mean 8.1 years' follow-up. Among 1,401 PWE, Gasparini et al. found that there was no difference in diagnostic delay between those who achieved seizure freedom (mean delay 6 years, standard deviation [SD] 9 years) compared with those who did not (mean delay 7 years, SD 11 years; $p = 0.7$).[76]

Similarly, a study by Parviainen et al. of 176 PWE found that diagnostic delay was not associated with seizure freedom ($p = 0.3$).[77] However, a large number of seizures before diagnosis was found to be associated with poor treatment response ($p < 0.001$). The authors therefore suggest that while diagnostic delay may not directly correlate with treatment response (say, if there is a long period between the first and subsequent seizures), diagnostic delay would have prognostic implications for a patient if seizures were frequent, and diagnostic delay represented patient or provider misdiagnosis.[77]

This view is supported by results from Pellinen et al., who compared 246 patients with subtle (non-motor) seizures and 201 patients with disruptive (motor) seizures.[78,79] Pellinen et al. found that not only did patients with subtle seizures have longer median diagnostic delay (616 vs 60 days, $p < 0.001$), 167 (68%) were not diagnosed until developing disruptive seizures, and 82.6% of potentially preventable motor vehicle accidents within the cohort were in those patients with undiagnosed subtle seizures ($p < 0.001$).[78,79]

Similarly, Kalilani et al. performed a retrospective cohort study on 59,970 PWE to explore the effect of the treatment gap on patient outcomes, where 36.7% of patients were found to be untreated up to 3 years after diagnosis.[80] Kalilani et al. found that lack of treatment was associated with higher risk of medical events (adjusted incidence rate ratio [aIRR] 1.2, 95% CI: 1.2–1.3), hospitalisation (aIRR 2.3, 95% CI: 2.2–2.3) and ED attendance (aIRR 2.8, 95% CI: 2.7–2.9).[80]

Delays between referral and assessment

One possible contributor to diagnostic delay is the time between a patient receiving neurology referral – say, from the ED – to actually being assessed in clinic. As described in section 3, guidelines recommend that first seizure patients should be reviewed by a neurologist within 2 weeks. However, the literature suggests that when patients are referred through “classical” community neurology clinics, these targets are often not met.

In a study by Fisch et al. evaluating the assessment of first seizures at a Swiss hospital, among 70 first seizure patients who were referred for classical community neurology follow-up, the average time to consultation was 50 days – substantially longer than the 2-week target.[81]

Similarly, in a study by Anang et al.[82] (elaborated on by Rizvi et al.[83]) of 51 first seizure patients at a Canadian community neurology clinic, the mean time to epilepsy specialist assessment was 80.1 days (SD 134.3 days) – again, substantially longer than the 2-week target.[83] Approximately 10% of patients experienced a wait time longer than 5 months from referral,[82] with the longest recorded wait time being 550 days.[82]

Despite these significantly extended wait times, Anang et al. concluded at the time of their study that referral processes were “timely” – although future research by the same authors, described in the next section, would go on to show that FSCs could significantly reduce these wait times.

7. First seizure clinics in assessment and management

Establishment and role of first seizure clinics

As described in preceding sections, the assessment and management of first seizures are complicated topics, yet with a need to act quickly and correctly to close the diagnostic and treatment gaps, and promote optimal patient outcomes. In order to address this complexity, “first seizure clinics” (FSCs), also known as “single seizure clinics”, have been suggested and implemented at secondary and tertiary hospitals in a number of countries.[84–86]

FSCs generally involve accepting referrals from EDs, GPs and hospital wards, to provide specialist epileptologist assessment for patients with an apparent first seizure, comprising the outpatient assessment and management described in section 3.[20] However, the exact referral sources, eligibility criteria and operations of each FSC vary from clinic to clinic. Some FSCs accept all patients with a potential first seizure, while others focus on episodes likely to be epileptic seizures or where the diagnosis is unclear.[20,83]

The notion of FSCs was developed in Australia, with the first FSC in the world being established in 1994 at Austin Health in Melbourne.[87] Elsewhere in Melbourne, FSCs have been established at the Royal Melbourne Hospital and Alfred Hospital since the late 1990s–early 2000s.[88,89] Literature from Australian clinicians and researchers, such as Seneviratne[90] in 2009, has long since recommended that first seizures be assessed in specialised FSCs.

In other countries, FSCs have only more recently begun to become increasingly established. For example, in the United Kingdom, a proliferation of FSCs has been observed following the publication of previously mentioned national guidelines in 2012, which recommend that first seizure patients receive specialist assessment within 2 weeks.[86]

The literature identifies 2 key roles that FSCs fill. Firstly, FSCs provide patients with access to specialised epileptologists with particular interests and experience in first seizures. This is of particular importance since, as described in section 3, the assessment and management of first seizures are complex topics, and distinct to the ongoing management of chronic epilepsy.[84]

Secondly, FSCs enable patients to access more rapid assessment pathways, to close the diagnostic and treatment gaps. As described in section 6, efficient assessment is important for improving patient outcomes, and the role of FSCs in this space is explored in the following subsection.

Accelerated access to neurology services

Preliminary evidence suggests that, compared with assessment in the general community, hospital outpatient FSCs have the potential to reduce patient wait times in the assessment of first seizures.

Rizvi et al. conducted a study comparing a prospective cohort of 200 first seizure patients referred to a Canadian FSC, with a retrospective "historic usual care" cohort from the previously cited Anang et al. study.[83] As described earlier, in the usual care cohort, the mean time between referral and neurologist assessment was 80.1 days (SD 134.3 days, range 0–550 days), over 4 times as long as the 2-week target recommended by guidelines.[83] In contrast, the FSC cohort received neurologist assessment in a mean 23.6 days (SD 20.3 days, range 2–134 days; $p < 0.0001$), substantially closer to the 2-week target.[83]

Rizvi et al. additionally found that the FSC pathway reduced mean wait time for an EEG from 37.1 days to a mere 4.0 days ($p < 0.0001$), mean wait time for a CT from 25.1 days to 4.6 days ($p = 0.003$), and mean wait time for an MRI from 81.3 days to 44.9 days ($p < 0.0001$).[83] These results represent large, significant improvements across key areas of assessment.

Fisch et al. report similar results from a prospective trial comparing a new FSC-based model with "standard" usual care,[81,91] finding that the FSC pathway significantly increased neurologist follow-up from 44% ($n = 31/70$) to 84% (95/113; $p = 0.0001$).[91] Median wait times were also shorter in the FSC group (15 days) than usual care (20 days).[91]

Additionally, among patients with a normal CT, 85% ($n = 56/66$) in the FSC group received an MRI, compared with only 52% (16/31) in the usual care group ($p = 0.0005$). Among the FSC patients with normal CT, MRI demonstrated epileptogenic abnormalities in 20% (11/56).[91] The mean wait time to MRI assessment was also reduced in the FSC group (12 vs 32 days, $p = 0.001$).[91]

Similarly, among patients with a normal routine EEG, 50% ($n = 33/66$) in the FSC group received a follow-up prolonged EEG, as recommended by guidelines, compared with only 5% (2/39) in the usual care group ($p < 0.0001$). Among the FSC patients with normal routine EEG, follow-up prolonged EEG was abnormal in 30% (10/33).[91]

These results demonstrate that FSCs can be effective at improving patient access to specialist assessment and optimal initial management of first seizures.

8. Uptake of first seizure clinic referrals

While the literature provides examples of improved administrative metrics among patients who attend FSCs, a key question remains whether referrals to FSCs themselves are well accepted by patients, or whether certain groups are less well served by current FSC referrals.[20]

Evidence from specialist clinics generally

Evidence from specialist outpatient clinics in general has suggested that a number of factors may be associated with nonattendance. Dantas et al. describe a systematic review of 105 studies, finding that increased nonattendance was found in a majority of studies to be significantly associated with demographic factors including younger age, minority groups (such as indigenous Australians and ethnic minorities) and lower socioeconomic status.[92] Notably, gender was found in a large majority of studies (70 of 90 studies) not to be associated with (non)attendance.[92]

Dantas et al. also found that increased nonattendance was associated with a number of clinical and administrative factors, including increased wait time, increased distance to the clinic, prior history of nonattendance, and specific clinical diagnoses and medical history (for example, with increased nonattendance in patients with depression).[92]

Dantas et al. note that studies have also demonstrated that patients without private health insurance are more likely to fail to attend specialist appointments.[92] While most of those studies have focused on the United States, where public health insurance coverage is more limited, similar results have been reported in Australia.[93] For example, Lalloo et al. found that public patients at a rural dental clinic were at higher risk of nonattendance compared with private patients.[94] Lalloo et al. suggest that this may be due to public patients generally being of lower socioeconomic status, and note that the public patients were less likely to have a recorded contact telephone number (82.6% vs 95.6%), which could make following-up on nonattendance more challenging.[94]

Attendance at first seizure clinics specifically

The evidence on patient (non)attendance at FSCs specifically is more limited. In a retrospective review by McIntosh et al. of all patients attending the FSC of one Melbourne metropolitan public hospital (*n* = 654), 8% of patients failed to attend the first appointment.[20] A different study by Manus et al. of 200 patients referred to a New Zealand FSC reported a similar nonattendance rate of 9.5%.[95] Neither study reported on characteristics associated with nonattendance.

These nonattendance rates are substantially lower than the nonattendance rates of 20.3%–42.0% reported in the Dantas et al. review among general neurology clinics in the community.[92] In contrast, a study by Palka et al. of 257 patients referred over 1 year to one FSC in the United Kingdom found a much higher nonattendance rate of 24.5% – closer to the rates reported by Dantas et al. – despite similar age and gender distribution to the McIntosh et al. and Manus et al. studies.[96]

The difference in reported nonattendance rates could be explained by differences in wait times, which, as described in the previous subsection, are known to be associated with nonattendance. In the Palka et al. FSC, the average wait time was “at least 6 weeks” due to demand exceeding

capacity,[96] whereas the median wait times in the McIntosh et al. and Manus et al. FSCs were 25 and 37 days, respectively.[20,95]

Additionally, Palka et al. found that, although nonattendance did not vary by age, gender or referral source overall, the combination of older age and female gender was associated with nonattendance.[96] Such subtleties could also potentially explain the discrepancy in nonattendance rates to some extent, but neither McIntosh et al.[20] nor Manus et al.[95] describe cohort demographics in sufficient detail to compare.

Furthermore, it cannot be excluded that differences in nonattendance could be contributed to by factors such as stigma, discrimination or patient education. Indeed, Palka et al. note that data such as ethnicity, religion and socioeconomic status were not available, and so the role of stigma could not be evaluated.[96] Further research is therefore required in this area, to assess whether certain vulnerable groups of patients are at higher risk of FSC nonattendance.

9. Outcomes from first seizure clinics

As explored in section 7, studies have demonstrated that FSCs have been associated with improvements in administrative metrics and timeline-based targets, such as time to specialist assessment and rates of follow-up.[83,91] However, what remains to be convincingly demonstrated is whether FSCs result in improvements to actual clinical outcomes, such as long-term seizure freedom and QoL.

Evidence on first seizure clinic outcomes

Very few studies have examined the effect of FSCs on longer-term patient outcomes broadly. One study by Hakami et al. examined the outcomes of 800 patients attending a Melbourne FSC over 9 years, finding that, of the patients with a first epileptic seizure, 124 (34%) went on to experience 1 or more recurrent seizures.[89] This is somewhat lower than the general long-term (>5 year) recurrence rates reported in the previously cited Krumholz et al. review of 39%–58%,[12] but without direct comparison of patient characteristics and follow-up periods, it is not possible to draw firm conclusions.

A study by Peterson et al. surveyed 393 PWE, and report that the highest QoL was found in patients who were “very satisfied” with access to their FSC (mean QoL score 67.69).[97] Progressively poorer QoL was found in patients “slightly satisfied” (mean score 45.53) and “not satisfied” (42.04) with FSC access.[97] Interestingly, patients “very satisfied” with FSC access had higher QoL than those who reported not requiring attendance at any FSC (mean score 60.93). This was despite the opposite being true across all other support services surveyed, where not requiring support was associated with the highest QoL.[97] However, Peterson et al. based their study only on

that subjective QoL index, and did not analyse any objective or specific measures, such as seizure freedom.

Overall, this evidence assessing the effect of FSCs on long-term outcomes is very limited, but combined with known benefits of FSCs on metrics such as reduced times to assessment or investigation, this does point towards potential long-term benefits of FSCs yet to be revealed.

Comparative evidence from other rapid access clinics

The position of FSCs may be compared with “rapid access clinics” in other specialties. For example, rapid access cardiology clinics have been established to accelerate assessment and management of patients referred from EDs, to meet guideline-based 2-week targets.[98] However, strong evidence directly comparing such clinics to other modes of care is also somewhat limited.

In a prospective study by Black et al. comparing one Australian rapid access chest pain clinic (n = 1914) to traditional community cardiology care (n = 435), median time to review was reduced from 45 to 12 days, and the proportion of patients diagnosed at the first clinic visit was increased from 32.0% to 100%. Over a 12-month follow-up, this translated into a reduction in unplanned ED attendances (from 12.9% to 5.7%) and major cardiovascular adverse events (1.4% to 0.2%).[99]

In gastroenterology, Nene et al. studied patients attending a new rapid access inflammatory bowel disease (IBD) clinic.[100] Nene et al. found that patients attending the rapid access clinic had a lower risk of hospital admission over the following 30 days compared with controls (4.5% vs 8.1%).[100] However, the control group comprised ED patients who “did not have access” to the rapid access clinic, and so may have represented a sicker population to begin with. Thus, the results may not be generalisable to comparing FSCs with historic community care.

In respiratory medicine, Flood-Page reports on the implementation of a rapid access chronic obstructive pulmonary disease (COPD) clinic in the county of Gwent, Wales.[101] The study is a descriptive analysis of regional administrative statistics, and involves no direct analysis of patient outcomes. However, Flood-Page reports that, after the clinic's implementation, hospital admissions for COPD exacerbation fell 8.8% in Gwent, compared with a 7.0% fall across Wales as a whole (p < 0.0001), with a similar positive effect for average length of stay.[101]

Conversely, Aslam et al. report negative findings from the field of oncology. In a study of 3,618 patients with colorectal cancer diagnosed over 8 years, Aslam et al. found that patients referred by a rapid access (“2-week wait”) pathway had shorter median overall survival compared with routine referrals (3.5 years vs 5.4 years, p < 0.001), despite receiving treatment quicker.[102] However, referral modes were not randomised, and patients referred by rapid access were 1.34 times as likely (95% CI: 0.98–1.54, p = 0.07) to have the most advanced (stage IV) disease.[102] Although this

difference is not statistically significant, it is likely the result was at least partly affected by selection bias, causing sicker patients to be preferentially referred by rapid access.

Overall, while there is scant literature comparing rapid access clinics to general community care, the evidence does point towards a potential positive impact by rapid access clinics, such as FSCs, on long-term patient outcomes.

10. Conclusion

The assessment and management of first seizure presentations are complex areas of clinical neurology. Seizures and epilepsy are conditions with significant impacts on patients, and are associated with large health burdens. Effective assessment and management are therefore of critical importance in optimising patient care and improving patient outcomes.

Our understanding, however, of factors such as comorbidities – particularly psychiatric conditions, and conditions with more distant or unclear causation – is limited and remains an area of active research.

Furthermore, evidence shows that historic usual care through general outpatient neurology clinics often fails to meet optimal timeframes, to the potential detriment of the epilepsy “treatment gap” and patient prognosis.

FSCs have been proposed and implemented in some countries, including Australia, to improve the assessment and management of patients with first seizures, but there is limited evidence on how well these clinics support the needs of different patient groups, and what effect they have on long-term outcomes.

Further research into these areas – the comorbidities and management needs of patients with first seizures, and the use and effects of FSCs – would be of significant benefit to optimising the care of these patients.

Research questions and aims

Research questions

- What comorbidities affect patients presenting to hospitals with first seizures?
- Does attendance following referral to FSC vary with demographic factors or clinical factors following a first seizure?
- Does attendance at FSC improve patient outcomes following a first seizure?
- Does the time between first seizure and attendance at FSC affect patient outcomes?

Research aim

To undertake a pilot study to determine if data linkage with administrative minimum datasets can yield insights into the above 4 questions.

Project outline

Overview and rationale

As described in the preceding literature review, there is a paucity of evidence surrounding the characteristics of first seizure patients, particularly with respect to less-well-studied comorbidities and associated management needs. Similarly, although FSCs have been established in Australia for over 2 decades, there exists only very limited evidence on patient uptake and long-term patient outcomes. A study examining these gaps in the evidence would accordingly be of great value to optimising patient care in first seizures.

In this project, it is proposed to use data linkage with administrative datasets to obtain the volume of data required to address the research questions. ICD-10-based coding in administrative datasets is known to be reasonably accurate for neurological conditions such as seizures and epilepsy,[103,104] with one study finding positive and negative predictive values of 90%–100%.[103] Studies with a similar methodology in the setting of seizures have been conducted by Martin et al.[69] and Blank et al.,[105] but have been limited to more restricted populations (such as older patients), have examined comorbidities and long-term outcomes only to limited extents, and have not evaluated the role of FSCs.

Proposed methods

Data linkage, inclusion and exclusion criteria

The investigators have conducted a retrospective survey of electronic medical records from 4 metropolitan Melbourne hospitals (including both public and private facilities), to identify ED attendances (the *hospital dataset*) between January 2008 and December 2017 with the ICD-10-AM code R56.8 (“Other and unspecified convulsions”), excluding any patients with a previous diagnosis of epilepsy.

At the 2 participating hospitals with longstanding FSCs, information on the patient's referral to and attendance at FSC, and the presence of epileptogenic and non-epileptogenic lesions on MRI, have also been identified as part of the hospital dataset.

The Department of Health Centre for Victorian Data Linkage (CVDL) has then extracted all records up to 31 December 2020 from the Victorian Admitted Episodes Dataset (VAED) and Victorian Emergency Minimum Dataset (VEMD) pertaining to the hospital dataset, and combined the results with the hospital dataset in a deidentified manner (the *combined dataset*). The VAED records demographic, administrative and clinical data from admissions to Victorian public and private

hospitals since 1993.[106] The VEMD records similar data from presentations at Victorian public EDs since 1999.[107]

For each patient in the combined dataset, the first recorded admission or ED attendance with the ICD-10-AM code R56.8 will be regarded as the *index seizure*. Any patient with a previous ICD-10-AM code of G40 (“Epilepsy and recurrent seizures”) or G41 (“Status epilepticus”) before the index seizure will be excluded. The resulting cohort will be the *first seizure cohort*.

Based on the first seizure cohort, the statistical analysis will comprise 4 related pilot projects addressing each of the 4 research questions. The statistical methods to be used in each pilot project are described in the next 4 subsections.

1. “What comorbidities affect patients presenting to hospitals with first seizures?”

Descriptive statistics will be used to characterise the demographic and clinical characteristics of patients in the first seizure cohort, including neurological history (e.g. stroke, TBI, CNS infection and dementia) and other comorbidities (e.g. IHD, cancer and psychiatric illnesses), based on ICD-10-AM codes shown in Appendix 1. The results will be compared with those previously reported in the literature.

Expected outcomes: To show that the comorbidities recorded in the first seizure cohort are, or are not, similar to those previously reported. If certain comorbidities are recorded at rates significantly different to those reported in the general population, the pilot analysis may support further research, such as a case–control study comparing comorbidities and risk factors in the first seizure cohort and age-gender-location-matched controls within the VAED/VEMD.

2. “Does attendance following referral to FSC vary with demographic factors or clinical factors following a first seizure?”

This pilot analysis deals with the subgroup of patients in the first seizure cohort, who were referred to either FSC at the 2 participating hospitals with longstanding FSCs (the *FSC cohort*). For each of those patients, the following *demographic variables* will be extracted: (D1) age, (D2) gender, (D3) whether preferred language is a language other than English, (D4) country of birth, (D5) Index of Relative Socio-Economic Disadvantage (IRSD) score of patient's residential area,[108] and (D6) distance between residential area and the FSC. The following *clinical variables* will also be extracted: (C1) triage category on presentation, (C2) whether other injuries were sustained at presentation, (C3) length of hospital stay, (C4) length of ICU admission, if any, and (C5) whether epileptogenic or non-epileptogenic lesions were identified on MRI.

Univariable Mann–Whitney (D1, D5, D6, C1, C3, C4) and Pearson χ^2 (D2–D4, C2, C5) tests will be used to investigate whether there is any association between each of the demographic or clinical

variables and whether the patient attended FSC. Any variables where $p < 0.2$ will be further tested in a multivariable logistic regression or generalised linear model.

Expected outcomes: To show that attendance does, or does not, vary with identified demographic or clinical factors. If attendance does vary, the pilot analysis may support the development of, and further research into, programs to support patients at high risk of non-attendance, and improve attendance following referral to FSC.

3. "Does attendance at FSC improve patient outcomes following a first seizure?"

This pilot analysis deals also with the FSC cohort only. For each of the patients in the FSC cohort, the following *outcome variables* will be extracted: (O1) the rate of subsequent ED attendance, (O2) the rate of subsequent hospital admission, (O3) the rate of subsequent seizures (ICD-10-AM code R56.8), and (O4) whether epilepsy was subsequently diagnosed (ICD-10-AM codes G40 and G41).

Zero-inflated Poisson regression (O1–O3) will be used to investigate whether there is any association between the incidence of each outcome variable and whether the patient attended FSC. Survival analysis (O4) will be used to assess whether there is any difference in time to subsequent diagnosis of epilepsy between patients who did and did not attend FSC. In order to investigate the effect of potential self-selection bias (e.g. where patients with less severe illness may be less likely to attend FSC), further analyses will also be performed stratified by the clinical variables C1–C5 described in the previous subsection.

Expected outcomes: To show that attendance does, or does not, correlate with improved patient outcomes. In either case, the pilot analysis may point towards areas worth further research, such as a future prospective study on patient outcomes from FSCs.

4. "Does the time between first seizure and attendance at FSC affect patient outcomes?"

This pilot analysis deals only with patients in the FSC cohort who attended FSC. For each of those patients, the time between the index seizure and attendance at FSC will be extracted.

For each of the outcome variables O1–O4 described in the previous subsection, zero-inflated Poisson regression (O1–O3) and survival analysis (O4) will be used to investigate whether there is any association between each outcome variable and the time between seizure and FSC attendance.

Expected outcomes: To show that increased time between seizure and FSC attendance does, or does not, correlate with poorer outcomes. As with previous subsections, the pilot analysis may inform future prospective research, and may inform programs to reduce delays between referral and attendance.

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Appendix 1: ICD-10-AM codes of conditions associated with seizures

Table 4. ICD-10-AM codes of conditions potentially associated with acute symptomatic seizures

Codes	Description
A17	Tuberculosis of the nervous system
A80–A89	Viral infections of the central nervous system
B69.0	Cysticercosis of central nervous system
C70–C72	Malignant neoplasms of brain and other parts of central nervous system
D33	Benign neoplasm of brain and other parts of central nervous system
E16.2	Hypoglycaemia, unspecified
E53.1	Pyridoxine deficiency
E72.9	Disorder of amino-acid metabolism, unspecified
E87	Other disorders of fluid, electrolyte and acid-base balance
F10–F19	Mental and behavioural disorders due to psychoactive substance use
G00–G09	Inflammatory diseases of the central nervous system
G35	Multiple sclerosis
G45	Transient cerebral ischaemic attacks and related syndromes
G93.1	Anoxic brain damage, not elsewhere classified
H34.1	Central retinal artery occlusion
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
N17–N19	Renal failure
Q28.2	Arteriovenous malformation of cerebral vessels
R56.0	Febrile convulsions
R73.9	Hyperglycaemia, unspecified
S02.0	Fracture of vault of skull
S02.1	Fracture of base of skull
S06	Intracranial injury

Table 5. ICD-10-AM codes of conditions potentially associated with remote and progressive symptomatic seizures

Codes	Description
A17, A80–A89, G00–G09, G45, G93.1, H34.1, I60, I61, I63, I64, S02.0, S02.1, S06	As per Table 4
A81.0	Creutzfeldt–Jakob disease
F00	Dementia in Alzheimer disease
F01	Vascular dementia
F02	Dementia in other diseases classified elsewhere
F03	Unspecified dementia
G30	Alzheimer disease
P37.1	Congenital toxoplasmosis

Table 6. ICD-10-AM codes of other conditions potentially associated with seizures

Codes	Description
C00–C97	Malignant neoplasms
D00–D09	In situ neoplasms
F20–F29	Schizophrenia, schizotypal and delusional disorders
F30–F39	Mood (affective) disorders
F40–F48	Neurotic, stress-related and somatoform disorders
G43	Migraine
G47.8	Other sleep disorders
H81	Disorders of vestibular function
I20–I25	Ischaemic heart diseases
R42	Dizziness and giddiness (including vertigo not otherwise specified)