Background:
A first unprovoked seizure is a sudden and unexpected life-event, occurring in 4% of the general population\(^1\). A prospective study from Iceland showed a mean annual incidence of 56.8 per 100,000 person-years for a first unprovoked seizure. Of these, 23.5 per 100,000 person-years had a single unprovoked seizure compared with 33.3 per 100,000 person-years who later developed epilepsy\(^2\). The numbers are considered representative for most developed countries. In another study\(^3\), the overall incidence of unprovoked seizures in both children and adults in Sweden was 60 per 100,000.

The overall risk of seizure recurrence following a single unprovoked seizure ranges from 27 to 71\(^{\%}\)\(^4\). The average risk of recurrence in a meta-analysis was found to be 40\% in prospective studies and 52\% in retrospective studies. The risk of recurrence is highest within the first weeks of the first seizure and decreases with time with about 80\% of recurrences occurring within two years of the initial seizure\(^5\). Risk factors for recurrence include the presence of a remote symptomatic etiology, abnormal neurologic examination, and the onset of seizure out of sleep. Positive family history of seizures or epilepsy and the presence or absence of Electroencephalographic (EEG) abnormalities have not been consistently shown to be correlated with the risk of recurrence\(^6\). The recurrence risk after a second unprovoked seizure is estimated at about 70\%\(^4\). Some studies have also shown that people with seizures/epilepsy are at high risk of premature mortality, with the risk being highest at onset of seizures\(^7\). Therefore, appropriate and timely assessment and investigation of these patients is essential in establishing the etiologies, ruling out treatable conditions and providing appropriate management especially in those at high risk of recurrence.
Brain-imaging and basic laboratory investigations are essential in ruling out obvious etiologies such as structural lesions and metabolic disturbances. An abnormal EEG has good predictive value. EEG changes are more likely to be found if completed in close proximity to the suspected epileptic event\textsuperscript{8}.

For the above reasons, there is an urgent need to properly assess and manage patients after a single unprovoked seizure with the goal of establishing the clinical diagnosis, determining if the patient has epilepsy by ruling out possible underlying etiology, determining the risk of recurrence, prognosis and the need for antiepileptic medication for patients at moderate or high risk of recurrence. Remote symptomatic seizures, family history of epilepsy, abnormal imaging and epileptiform abnormalities all increase the risk of recurrence and therefore the likelihood of needing treatment after a single event\textsuperscript{9}.

**Objectives:**

To investigate the wait times to completion of medical assessment of single unprovoked seizure patients referred to a local epilepsy clinic. Another goal was to evaluate the safety of the referral and assessment process. These would help determine if wait times for medical assessment and investigations have any impact on the outcomes of first unprovoked seizures.
**Materials and method:**

A retrospective chart review from the epilepsy clinic (run by a single epileptologist) of a provincial neurological referral center in Saskatchewan was performed over a period of 3.5 years (2007 – 2010). Institution review board waiver was obtained. Data was collected on all patients referred to the epileptology clinic. Clinic charts from a database classified as single seizure were included. Initially 70 cases were identified for the said period. 51 of the reviewed charts fulfilled the criteria for a single unprovoked seizure. 19 were excluded from the study; some had presented with a status epilepticus and in others, a review of history and hospital records revealed that they had a prior history of seizures or a known seizure disorder. Patients with provoked seizures (known cause of seizure, for example metabolic or electrolyte disorders) were also excluded. Information collected on driving, was based on review of hospital charts and ambulatory care notes written by primary care physicians and patient’s account on whether or not counseling regarding driving (including any driving restrictions) had been provided. Given the retrospective nature of this study, the motor vehicle licensing department could not be contacted without informed consent for verification.

Data gathered included: Age of patient, date of single seizure/spell, date of initial assessment, the initial assessment and impression, specialty of physician performing initial assessment, date of referral to the epileptologist, date seen by epileptologist and wait times for imaging, computed tomography (CT) and magnet resonance imaging (MRI) of the brain and EEG from time of event. Median and mean wait times were determined and the final diagnosis by the epileptologist was compared to the initial
impression of the referring physician. Seizure recurrence during the wait times or during the assessment period was considered a major adverse event and associated injuries were classified as minor if they resulted in no significant bodily harm (bruising etc.) requiring no medical attention or treatment and as major if bodily harm (fractures etc.) was obvious requiring medication attention. Apart from the above, other safety variables included abnormal EEG and abnormal MRI findings considered predictive of a higher risk of seizure recurrence. Microsoft Excel and SPSS software were used to analyze collected data.

Results:
Fifty one patients were included. Median age at single seizure was 41 years (range 16–81). The gender distribution was 51.9 % (28) male and 48.1 % (23) female. Figure 1 shows the distribution of events across the different age groups.
Figure 1: Age Distribution Chart

The description of the spell was consistent with seizure in 90.7% (48), syncope in 3.9% (2) and migraine variant in 1.9% (1) of cases. The three seizures types described were generalized tonic-clonic seizures (grand mal) in 93.8% (45), complex partial seizures in 4.2% (2) and tonic seizures in 2.1% (1) of presumed seizures.

Median wait times to see the epileptologist was one month from either time of single seizure or time of referral. 54.9% of patients were seen within 2 months and 98.5% within 6 months of initial event by the epileptologist.

The median wait time for EEG was 1.5 months (0 – 14.5), 59.6% of the EEGs were performed within 2 months and 75% within 7 months from the initial event. Mean wait time for CT scan -head was 5 months (0 – 22), 55% of these were performed within 48 hours of the event. Median waiting time for brain MR-imaging was 5 (0 - 36) months; 59.3% MRIs were completed within 6 months of event.
Figure 2: Wait times for investigations and epileptologist (initial event versus referral)

The initial assessment was performed in 42.6% by an ER physician, 25.9% by a family physician, 7.4% by an internist, and 14.8% by a general neurologist. In 3.7% of cases the specialty of the initial assessing physician was unknown.

Figure 3 shows the median wait times to see the epileptologist as a function of the referring physician. Patients referred by either an emergency physician or an internist had the shortest median wait times while those referred by another neurologist longest wait times.
The diagnosis of seizure disorder by the epileptologist differed only by 9% from the original assessment performed by the referring physician, representing a high degree of convergence (91%). Of all 51 cases reviewed; 4 diagnoses were altered after assessment by the epileptologist. Two cases previously considered possible syncopes were diagnosed with primary generalized epilepsy. One diagnosis of possible migraine was changed to primary generalized epilepsy and one diagnosis of seizure disorder was inconclusive (possible migraine variant). The later was not excluded from the study. Anti-epileptic medication was initiated in 20.4% of patients prior to referral. Most frequently used antiepileptic drugs (AEDs) were phenytoin (33%) and lamotrigine (27.8%). The decision to treat was attributed to concerns for seizure recurrence in
16.7%, EEG abnormalities in 18.5%, abnormal imaging findings in 13%, and other reasons in 51.8%. The reasons for starting AEDs are shown on table 1.

<table>
<thead>
<tr>
<th>Reason</th>
<th># of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG abnormalities</td>
<td>10</td>
</tr>
<tr>
<td>MRI abnormalities</td>
<td>2</td>
</tr>
<tr>
<td>CT abnormalities</td>
<td>5</td>
</tr>
<tr>
<td>Seizure recurrence</td>
<td>9</td>
</tr>
<tr>
<td>Other reasons*</td>
<td>13</td>
</tr>
</tbody>
</table>

*Other reasons:
- job as fireman
- desire to resume driving
- two generalized tonic-clonic seizures in 24 hours
- developmental delay
- violent seizure
- history of head injury (not seizure related)

Table 1: Reasons for initiating AEDs after 1st unprovoked seizure

A positive family history of seizures was reported in 22.2% (12 patients), childhood seizures and/or febrile seizures in 9.3% (n = 5), history of head trauma and/or CNS infections in 14.8% (n = 8). Alcohol and illicit drugs were considered possible triggers in 7.4% and 3.7% of cases respectively.

Seizure recurrence was noted in 25.5% (13 of 51) after a follow-up of at least 12 months. 46.2% of these patients showed imaging abnormalities while 38.5% had abnormal EEG findings. 29% of patients started on AEDs had both abnormal EEG and imaging findings, 29% had abnormal EEG only and 19.5% had abnormal imaging only. Seizure recurrence was 28.2% (11 of 39) in patients with normal CT head and 16.7% (2 of 12) in patients with structurally abnormal CT head. Normal and abnormal EEGs were associated with recurrence rates of 26.7% and 23.8% respectively. The EEGs of two
patients with focal slowing were considered abnormal, although no other epileptiform features were observed. Abnormal MR-imaging was associated with a recurrence rate of 25% (4 of 16) and in those with both abnormal MR-imaging and EEG, the recurrence rate was only 10% (1 of 10). Table 2 shows the different EEG patterns (patients who had more than one EEG are also included). Figure 4 shows the distribution of seizure recurrence across the different age sub-groups.

Past history of febrile or childhood seizures was associated with a recurrence rate of 40% compared with 25% for those with prior CNS infection or head trauma, 41.78% had positive family history of seizure, 50% had a history of illicit drug use or alcohol intoxication. Seizure recurrence rate was 41.6% (5 of 12) in patients with a positive family history and 20.5% (8 of 39) in those with a negative family history for seizures.

<table>
<thead>
<tr>
<th>EEG findings</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Spikes</td>
<td></td>
</tr>
<tr>
<td>Generalized spike and wave</td>
<td>11</td>
</tr>
<tr>
<td>Right temporal spikes</td>
<td>1</td>
</tr>
<tr>
<td>Right frontal spikes</td>
<td>2</td>
</tr>
<tr>
<td>Bilateral temporal spikes</td>
<td>2</td>
</tr>
<tr>
<td>2 Slowing</td>
<td></td>
</tr>
<tr>
<td>Left TIRDA</td>
<td>1</td>
</tr>
<tr>
<td>Right frontal slowing</td>
<td>1</td>
</tr>
<tr>
<td>Left temporal slowing</td>
<td>1</td>
</tr>
<tr>
<td>Generalized slowing</td>
<td>2</td>
</tr>
<tr>
<td>3 Other patterns</td>
<td></td>
</tr>
<tr>
<td>Breach rhythm</td>
<td>2</td>
</tr>
<tr>
<td>Triphasic waves</td>
<td>1</td>
</tr>
<tr>
<td>4 Normal</td>
<td>29</td>
</tr>
</tbody>
</table>

* EEG report missing in one case

Table 2: EEG findings and distribution of documented abnormalities
During the waiting period, minor injuries (bruising) were reported in two patients, there were no reported mortalities. Formal documentation on counselling about driving restrictions and reporting of patients following seizure or seizure-like events by primary care physician to the driver’s licencing authority as mandated by provincial legislation in the province of Saskatchewan could only be found in 3% of cases.

Discussion:

We found that 98.5% of patients in the district were seen by the epileptologist within 6 months and that during the waiting period there were no case fatalities, and only 2 cases of minor seizure-related injuries (due to seizure recurrence). These findings suggest that patient referral and assessment is being done in a safe and relatively
timely and fashion given the otherwise long wait times for neurologists in the province. We consider the wait time from time of event to time the patient was seen by the specialist to be excessively long, not albeit comparable to the data from the National Clinical Audit of Epilepsy-related death from the UK\textsuperscript{10}, where only 69\% of referrals were completed within 1 week and 15\% completed in 1 – 6 months by the general practitioner and 15\% of individuals having to wait more than 6 months for specialist appointments. This pattern with significant delays in the referral process is reflected in our study and some cases with extremely long wait times from time of event could be attributed to lack of knowledge about the referral process by primary care physicians or an attempt to manage by same. The establishment of a first seizure clinic with clear referral guidelines would reduce this unnecessary delay and make the process more efficient and safer. Some centers around the world have already adapted this approach and in Edinburgh, 72\% of suspected first seizure patients were offered an appointment within six weeks of referral\textsuperscript{11}. Seizure recurrence was highest in the age group younger than 20 years and also slightly higher in those older than 70 years. This finding is similar to that reported in the UK National General Practice Study of Epilepsy with highest recurrence in patients under the age of 16 and those older than 59 years\textsuperscript{12}. Early seizure frequency, etiology of seizures, an abnormal EEG are known to be significant predictive factors for seizure recurrence and long term outcomes as observed in the MESS trial\textsuperscript{13} and a long term follow-up study\textsuperscript{14}, recurrence in our study was altered by the early use of AEDs in patients with abnormal EEGs and/or abnormal MRIs. The diagnostic and prognostic significance of a single routine EEG with 12 – 27\%
sensitivity\(^3\); improved by 15\% if done within 24 – 48 hours of event and further by 23 – 50\% with sleep deprivation\(^ {15,16,17}\), but lower in this study most probably due to the delay in obtaining investigations, especially EEG within the specified interval of highest yield as less than 50\% of EEGs were completed within one month from the time of the initial event and very few within 24 – 48 hours of the event.

The high rate of neuroimaging and EEG abnormalities in this study most likely reflects the highly selective nature of the group; considered high risk for seizure recurrence or likely focal seizure in origin, as not all patients with first unprovoked seizures are referred to the epileptologist in the province of Saskatchewan.

The occurrence of single unprovoked seizures has psychosocial implications for patients and families and concerns about etiology and likelihood of recurrence often impact life-style areas such as driving restrictions and restrictions in work, family and leisure activities\(^ {18}\). Although in this study there was no reported mortality or significant injuries from the event or subsequent recurrence, the professional, financial and psychosocial impact cannot be underestimated (no conclusion can be drawn from our data as this was not the subject of investigation in this study).

There was a significant delay in obtaining even basic imaging (CT head) with only 50\% scanned within 24 hours most likely due to unavailability of scanners in some parts of the province.

Retrospective, prospective and randomized controlled studies in both adults and children have provided data showing that early seizure recurrence is reduced by early initiation of anticonvulsant treatment, but this intervention does not alter the prognosis for the development of epilepsy. The risk of recurrence is increased with abnormal
imaging, epileptiform changes on EEG, positive family history of epilepsy and remote symptomatic seizures. These factors might increase the likelihood of AED use after a single event reflecting the reasons for the early initiation of AED in our patients. Although the American Academy of Neurology does not recommend treatment with AED for the prevention of the development of epilepsy following first unprovoked seizure (level B), the guidelines suggest considering the use of AEDs where the benefits of second seizure risk reduction outweighs the risk of pharmacologic and psychosocial side effects. Overall, AEDs were started in 74.1% of first unprovoked seizure (only 25% recurrence rate in this subgroup). About 20% of these cases where started on AEDs by the primary care physician, the overall use of AED is higher than would be expected, but this is not different from that reported by Hauser et al. A possible explanation would be that the cases referred to the epileptologist represent higher risk patients when compared to general population of patients with single unprovoked seizures. This is further supported by the high incidence of EEG- and imaging abnormalities in this study. A significant number of those patients with abnormal imaging or EEG findings were started on AEDs. This is the most likely explanation for the lower rate of seizure recurrence in this group. Consequently, as previously reported in other studies, we consider abnormal EEG to be a good predictor of seizure recurrence, but it might have been masked in this study by the early used of AEDs. In our study, predominantly first generation antiepileptic drugs were used; phenytoin and lamotrigine.

The low rate of reported driving restrictions by the primary care physician shows lack of awareness and probably lack of knowledge about the implications of a single seizure.
This aspect has to be improved in a province like Saskatchewan where a mandatory written report to Saskatchewan Government Insurance (SGI) is required after a seizure. A better education of family practitioners and ER physicians about the social, occupational and health implications of a single unprovoked seizure is required in the future.

**Conclusions:**
We conclude that the regional referral process of patients with a single unprovoked seizure is timely. Although there were no case fatalities, due to the limitations of this study as mentioned below, safety issues need to be addressed in a prospective study. The wait times are longer than we had expected and the process is slower than recommended in most guidelines. Education of primary care physicians is important to avoid unnecessary delays and mismanagement of patients. Further improvements are needed to increase access to investigations (especially EEG, CT and MRI) with the ultimate goal of maximizing diagnostic yield and hence ability to stratify the patients for risk of seizure recurrence. We suggest the establishment of a first/single seizure clinic as well as clear referral guidelines as the best approach for these patients. A larger study (preferably, a prospective study with direct recruitment of patients from the emergency departments) involving several referral centers is necessary to evaluate the timeliness and safety of referrals of first unprovoked seizures in the Canadian medical system.
Limitation:

This was a retrospective chart review that only captured patients referred to the epileptologist and as such does not reflect the outcome of those patients referred to other neurologists or physicians in Saskatchewan. Secondly, the wait times were calculated from the date of initial event or referral until the date of assessment or date on which the test was performed and we did not take into consideration if any previous appointments were missed by the patient. It is also possible that a patient referred to the clinic could have died prior to his scheduled appointment and due to the limitations of the database would not be captured in our study. Finally, the conclusions made from this review are limited by the small sample size, the findings may not generally apply to all single seizure patients in the Province of Saskatchewan and beyond.

- Poster presented at the American Epilepsy Society Meeting in San Antonio, USA, December 2-7, 2010 Epilepsia (Abst. 2.347)

References: