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Use of an online epilepsy diary to characterize repetitive seizures

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ABSTRACT

Significance: Little is known about patterns of seizures that occur multiple times a day, sometimes called clusters or serial seizures.
Objective: The online diary, My Epilepsy Diary (MED), provided self-reported data from community-based patients to describe the characteristics of clusters.
Methods: We used MED data to define a population of 5098 community outpatients, including 1177 who specified time of multiple seizures in a 24-hour period.
Outcomes included cluster prevalence and frequency, distribution of interseizure time intervals, as well as the types of triggers commonly reported.
Results: One-fourth of days with any seizures included clusters for these patients. Most days with clusters included 2 seizures, with >5 events occurring in only 10% of days. One-third of seizures occurred within 3 h of the initial event and two-thirds within 6 h. When more than 2 seizures occurred, the time to the next seizure decreased from an average of over 2 h (to the 3rd event) to a quarter-hour (from the 4th to the 5th event).
Conclusion: My Epilepsy Diary data have provided the first overview of cluster seizures in a large community-based population. Treatments with less than 3-hour duration of action would be bioavailable at the time of only one-third of subsequent seizures. Although limited by the self-reported and observational nature of the diary data, some general patterns emerge and can help to focus questions for future studies.

1. Introduction

The prevention of a series of seizures (clusters), particularly in conjunction with known precipitating factors, was the "most intelligent and least investigated application of acute drug administration" according to a past president of the International League Against Epilepsy [1]. For patient safety, recognition of a cluster pattern provides an opportunity to prevent or protect against the next seizure. For clinicians, understanding that a patient often experiences clusters of events suggests the need for a rapid-acting treatment that could be used when multiple seizures are anticipated. Development of protective strategies is limited by imperfect knowledge about prevalence, timing, variability, and other details of clusters (see review by Haut [2]).

1.1. Definition of multiple seizure events

No standard definition of seizure clusters is universally accepted. Approaches can be divided into clinical and statistical [3]. A clinical definition specifies a minimum number of seizures during a particular interval of time, for example, 2 seizures within 4 h or 3 seizures within 24–48 h [4–7]. This type of criterion is simply applied, but it does not account for the large variability in seizure frequency among different patients. Individuals with high daily seizure frequencies would experience clusters every day, and those with annual seizures would not register a cluster of 3 seizures in a week. Statistical definitions of clusters describe a significant increase (e.g., 3- or 4-fold or 3 standard deviations) in seizure frequency compared with earlier times. This earlier time can be taken as the frequency for the prior day [8], prior 3 days [2], or some other time interval before the cluster. The precluster interval can be defined in relation to the average seizure-free interval for that individual. A more global method ascertains whether the time distribution of seizures is representative of a random Poisson process [9]. If not, then a nonrandom factor, such as clustering, is likely to be in effect.

An operational definition of "acute repetitive seizures (ARS)" was developed for clinical trial entry criteria. The rectal diazepam clinical trial [10] defined ARS as "an episode of multiple complex partial or generalized (tonic, clonic, tonic–clonic, atypical absence, or myoclonic) seizures occurring within a 24-hour period in adults or a 12-hour period in children, with a pattern distinguishable from the patient's usual seizure pattern." A study of intranasal midazolam (USL261) in subjects with a history of seizure clusters defined a time frame for success as being no

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further seizures from 10 min to 6 h after drug administration (http://clinicaltrials.gov/ct2/show/NCT01390220?term=USL261&rank=4).

An alternative approach is to signify clusters as more than one event occurring within a specific time period. A broad definition could include any 24-hour period or calendar day during which two or more seizures occurred. The inception of mobile electronic diaries makes it feasible for patients to record events after individual seizures with an electronic time stamp. This allows for analyses based on 24-hour intervals.

1.2. Prior diary studies

Studies of patients who have clusters of seizures have mostly been small and short-term. In contrast, web and mobile-based epilepsy diaries [11–13] provide novel opportunities to gather self-reported seizure cluster information on very large populations of people with epilepsy. My Epilepsy Diary (MED), developed by the Epilepsy Therapy Project (now conjoined with the Epilepsy Foundation) and Irody, Inc., is a resource used by approximately 30,000 people with epilepsy. Longitudinal data collected directly from patients over long periods can be used to assess seizure patterns as well as treatments. In this report, we have used diary data that include event times to describe the characteristics of clusters among community-based people with epilepsy.

2. Methods and procedures

My Epilepsy Diary (MED) is an anonymized web and mobile-based service provided to individuals with epilepsy. The diary is available for global use in four languages — English (dialects for the US, Australia, and Canada), Italian, French, and Spanish. All information is entered by the consumer or family. The core of the diary is a digital calendar (Fig. 1).

The information in this report derives from data downloaded from 28,697 patients with information in the diary. All data were anonymous and not identifiable to any individual. In keeping with data protection guidelines, names and locations are not collected. Users are asked to volunteer minimal demographic information, such as age, age at onset, and gender. Self-identified seizure types, medication names, and doses are recorded by users.

Users provide information about seizures, including type, frequency, time, duration, and triggers. Other entry elements available to users include mood, medication regimens for that day or for medication refills, missed or extra doses of medicines, and an opportunity for free text write-in or attachment of digital files and videos. When a user labeled an event as a cluster without identifying individual seizures because they were too numerous to count, it was labeled as an unspecified

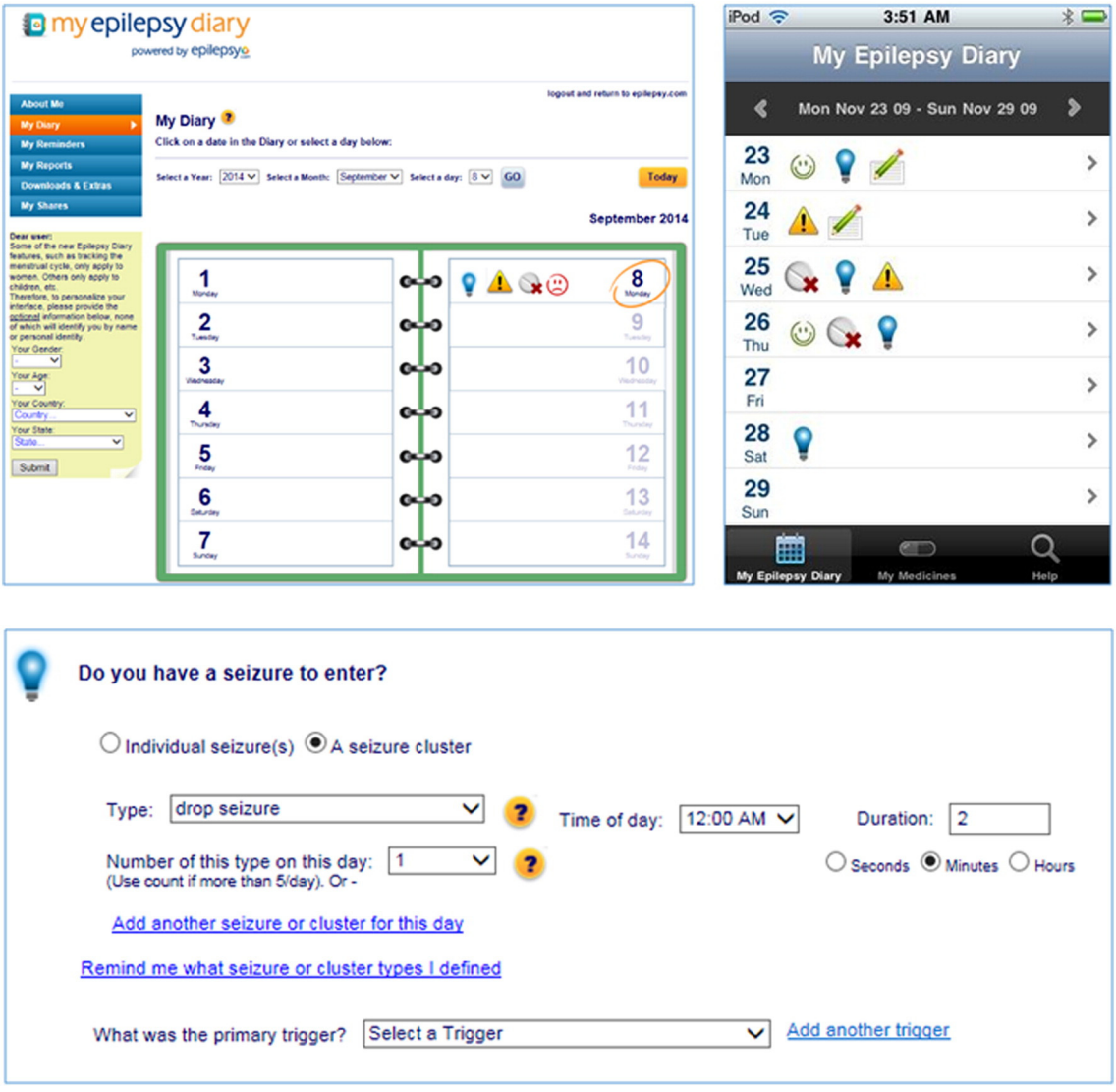

Fig. 1. View of entry screens for My Epilepsy Diary. The upper left side shows a web view of one week of calendar data. The upper right side shows calendar entry for a mobile smart phone. The lower segment depicts entry choices for individual seizures or clusters.

cluster. For purposes of this paper, we define a cluster as two or more seizures in a midnight-to-midnight calendar day in order to have the most inclusive definition to allow data capture for further analysis. The unspecified clusters were used to calculate prevalence of clusters but not interseizure time intervals.

2.1. Patient selection

The data set included patients with clusters (2 or more seizures reported in a 24-hour period: 12:00 am–11:59 pm) (Table 1). Days with only one seizure were not included. Events designated by the user as a "cluster", without specifying the actual number or time of day of the individual seizures, were analyzed separately from clusters of 2 or more specified seizures, since the former could not be used to calculate interseizure time intervals. These are referred to as unspecified clusters, and they occurred on 13.1% of days when any seizure was reported. Data were collected in a spreadsheet for descriptive statistics (mean, SD, and median). Additional analyses were performed with t-tests using a two-tailed distribution, with the assumption of independent samples of equal variance. Outcomes included cluster prevalence and frequency, distribution of interseizure time intervals, and types of triggers commonly reported.

IRB approval was not required, because no medical relationship existed between subjects and investigators. Subjects using MED gave permission at time of enrollment to use anonymous data for research.

3. Results

Between MED inception in October, 2009 and that in February, 2014, a total of 28,697 unique user IDs showed MED activity, generating 1,438,367 records. Clinical trials using MED included an additional approximately 400 patients (not included in these analyses). The number of patient days in the diary was 546,768, averaging 70 (median = 19) diary days per patient. Mobile devices were used for data entry in 62%. The minimum period of diary use to be included in analyses was 60 days, chosen somewhat arbitrarily to correspond with a common practice of reporting monthly seizure frequencies. Diary records less than two months might be expected to miss clusters. Some patients reported more than four years of seizure logs. Among the users were 5018 patients (17.5% of all unique users) who reported 29,341 seizures occurring as clusters. This cohort provided a mean of 40.6 seizures (median = 7) per person over the individual's period of use of the diary.

IRB approval was not required, because no medical relationship existed between subjects and investigators. Subjects using MED gave permission at time of enrollment to use anonymous data for research.

Table 1
Demographic characteristics of the analyzed study population.

Characteristic	Number
Gender (N = 1522 overall)	F = 46% M = 30% Unknown = 24%
Age in years at seizure onset (N = 1522 overall)	0–1 = 6 1–10 = 95 10–20 = 126 20–30 = 183 30–40 = 2 Unknown = 1110
Number of unique patients included in the demographic analysis	1522
Total patient days listing time between seizures	6844
Unique patients with clusters within 24 h	1177
All seizures included	22,650
Average number of seizures per patient	19.242
Average patient days in diary	85.556

3.1. Description of diary users

Demographic information was limited to the 10% of users who completed that optional section. Their ages ranged from less than 1 year to greater than 70 years, with almost twice as many female users as male. Most patients reported age at seizure onset prior to age 30.

From this cohort, we identified 1177 patients who recorded more than 1 seizure in a 24-hour period. The most common number of events on cluster days was 2 seizures per 24 h, with declining prevalence for 3, 4, 5, 6, 7, and 8 seizures per 24 h (See Table 2). Approximately 90% of days with clusters contained 5 or fewer seizures. Over the course of their diary use: 1978 had only 1 cluster, 741 had 2 clusters, 437 had 3 clusters, 291 had 4 clusters, and 1570 had 5 or more clusters. Outliers included 159 users reporting more than 50 seizure clusters.

Clusters also may be characterized by the number of days on which a specific number of seizures occurred. Days with 1 seizure totaled 28,762; with 2, 6140; with 3, 1660; with 4, 640; and with 5, 680, among 37,882 total days with seizures. Days with 2–5 seizures accounted for 24.1% of the total days of seizures. Some patients experienced multiple days with clusters.

3.2. Seizure frequency

Patients with clusters had a higher daily seizure frequency ($n = 1023$, mean $= 0.14 \pm 0.22$) than did those who never reported more than one seizure during a 24-hour calendar day ($n = 2621$, mean $= 0.01 \pm 0.20$, $p < 0.005$).

3.3. Time intervals between seizures

Time of day for individual seizures was entered for 28,618 patient days with clusters, allowing calculation of the interseizure interval. The mean elapsed time from the first to the second seizure was 131 ± 149 min ($n = 6797$), 46 ± 59 min between the second and third events ($n = 2233$), 21 ± 29 min between the third and fourth events ($n = 942$), and 12 ± 14 min between the fourth and fifth events ($n = 438$). Among days with at least 2 seizures, one-third of the seizures occurred within 3 h and two-thirds within 6 h of each other. Distribution of interseizure intervals is shown in Table 3 and Fig. 2.

Most sequential events occurred within 3 h (55.6%) on 72.1% of days. After the initial event, 25.5% of sequential seizures occurred within 3 h on 29.5% of days.

3.4. Triggers for clusters

Perceived triggers (precipitating factors) for seizures associated with clusters were listed for 12,696 events (Table 4). Among the cluster precipitants described, 28% were related to sleep, waking, or sleep deprivation. Stress, menstruation, missing or changing medicines, illness, alcohol, or nonmedical drugs were also listed as common triggers.

Table 2
Number of seizures occurring a specified number of times per day.

Number of seizures in 24 h	Number of seizures meeting the criteria
2	5701
3	2226
4	1014
5	892
6	291
7	199
8	174
9	244
10	234

Table 3
Numbers of sequential seizure pairs categorized by time interval between seizures.

Minutes	Number of seizures (for days with ≥2 seizures)	Cumulative % less than the maximum time in the interval
<10	5	0.07%
11–30	438	6.4%
31–60	409	12.5%
61–120	818	24.4%
121–180	852	36.9%
181–360	1929	65.0%
361–720	1762	90.8%
721–1440	631	100%
Total seizures	6844	100.0%

Table 4
Precipitating factors for seizure clusters.

Trigger	Number	Percentage [a]
I don't know	3815	30%
During sleep or when waking up from sleep	2273	18%
Mood/stress	1512	12%
Other	1404	11%
Sleep deprivation or lack of adequate sleep	1257	10%
None	746	6%
Menstrual period	527	4%
Missed medicine or medicine changes	513	4%
Sick with fever or other medical problems	371	3%
Drinking alcohol or using nonmedical drugs	158	1%
Total	12,576	100%

[a] Some patients reported multiple triggers.

3.5. Missed or extra medications

Among patients taking an extra medicine for clusters, the most common medications were clonazepam (42%) and lorazepam (17%). Extra medicine was taken on 1145 days with clusters; medicine was missed on 1264 cluster days, and both missed and extra medicines were taken on 109 cluster days. Missing a medication was reported on 3.4% of total days with clusters. An extra medication was taken on 3.1% of total cluster days. Lamotrigine (15%) and levetiracetam (12%) were most often listed as medications missed.

3.6. Modeling different definitions of seizure cluster

The prevalence of seizure clusters would have varied with different definitions of clusters as displayed in Table 5, which models the outcomes of various possible definitions of clusters. A patient day is considered to contain a cluster if the requisite number of seizures occurred in a 24-hour period, as hypothetically defined in the left column of the table.

4. Discussion

These descriptive data from longitudinal patient diaries provide an overview of how often community-based patients have multiple seizures within a day. The large population who recorded events and medications also shows how patients respond when experiencing or anticipating multiple seizures. Previous studies using diary recordings from clinic populations were, of necessity, limited to relatively small numbers. In contrast, our web-based diary included seizure information from approximately 30,000 patients. These data reveal that 17.5% of the patients using the diary experienced clusters, occurring on 13% of days when any seizure was reported. One-fourth of days with any seizures included clusters for these patients. Most days with clusters included two seizures, with more than five events occurring in only 10% of days. One-third of seizures occurred within 3 h of the initial event. When more than two seizures occurred, the time to the next seizure decreased from an average of more than 2 h (from the 1st to the 2nd event) to less than a quarter-hour (from the 4th to the 5th event). The timing of events suggests that a short-acting drug could be a useful acute treatment for prevention of multiple seizures among patients who often experience clusters.

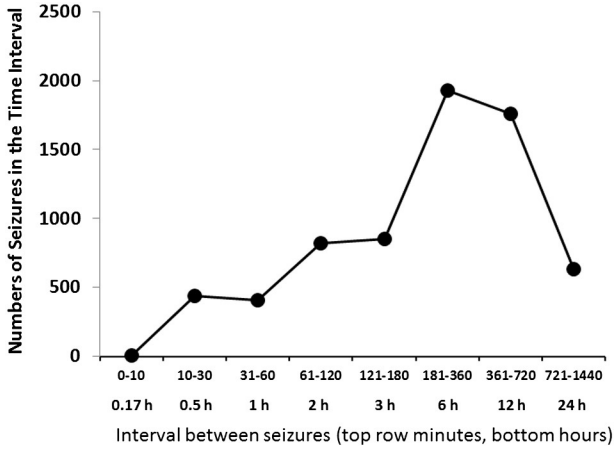

Fig. 2. Serial seizure interval. The number of clusters occurring within a specified time interval.

4.1. Limitations

Interpretation of our findings is limited by the observational and uncontrolled nature of the data and the unmonitored subjective reporting of events considered by the patient or family to represent seizures. Some reported events likely document imitators of seizures. The role of precipitating factors cannot be accurately interpreted without knowing how often those factors occurred with an accompanying seizure cluster. Individuals with clusters, or with high seizure frequencies that tend to correlate with having clusters, may be more inclined to maintain an accurate diary, thereby inflating the population prevalence of clusters. Future prospective studies with biometric devices [14–19] or implanted EEG monitors [20] may improve accuracy of seizure tracking.

4.2. Prevalence of seizure clusters

Prevalence of seizure clusters depends upon the definition of clusters, the population being studied, and the quality of information on

Table 5
Modeling alternative definitions for serial seizures.

Definition	Prevalence of patients[a]	Prevalence of patient days
Seizures/24 h	% of patients having ≥2 seizures in 24 h	% of days on which seizures occurred ≥2 times
2 in 24 h	36.5% (N = 1865)	52.5% (N = 5121)
3 in 24 h	19.1% (N = 976)	19.6 (N = 1907)
4 in 24 h	8.4% (N = 430)	8.8 (N = 856)
5 in 24 h	8.1%(N = 413)	7.7 (N = 750)
≥6 in 24 h	27.8% (N = 1421)	11.4% (N = 1112)
Total/24 h	100% [a]	100% [a]
Seizures/h [b]	% of patients having ≥2 seizures within interval	% of days on which seizures occurred within interval
≥2 in 1 h	6.8% (N = 299)	7.0% (N = 647)
≥2 in 2 h	9.7 (N = 424)	11.8 (N = 1090)
≥2 in 3 h	9.0 (N = 395)	10.7 (N = 988)
≥2 in 4 h	8.2 (N = 357)	9.6 (N = 884)
≥2 in 5 h	7.9 (344)	8.4 (771)
≥2 in 6–11 h	36.9 (1614)	35.8 (3307)
≥2 in ≥12 h	21.6 (945)	16.7 (1546)

[a] Patients can be counted more than once.
[b] Includes only seizures listed with a specific time of day in the diary.

seizure occurrence. Paper or electronic diaries are mainstays of clinical epilepsy management and of therapeutic trials [12]. One small diary study of patients with intractable epilepsy [8] found clustering in 10 of 13 patients. Milton and Gotman [21] evaluated 24 patients keeping a seizure diary for a mean of 237 days. The range of seizures logged was 5–76, with a mean of 18, which represents 0.076 seizures per day. Half of the patients had a nonrandom pattern of seizure occurrence, but only 3 of the 24 showed clustering by their definition. A prospective diary study in 87 diary-compliant patients [3] defined seizure clusters in two ways. The first was a clinical definition of three or more seizures in 24 h. The second was a statistical definition of degree of divergence from a random Poisson distribution. The median seizure rate was 0.07 ± 0.5 seizures per day. Seizure frequency was 10-fold higher for individuals who exhibited seizure clusters by either of their definitions. The clinical definition was met by 43% of the subjects and the statistical definition by 22%. All subjects who satisfied the statistical definition also satisfied the clinical definition. Our diary data also showed higher seizure frequency rates among patients with clusters compared with those with only single seizures in a day.

A review of seizure clusters by Haut [2] tabulated a 10-fold prevalence range of 7–76%. Another study with a follow-up of 37 years evaluated 120 patients with childhood-onset epilepsy [22], finding 22% with clusters. Our prevalence numbers for seizure clusters fall within the wide range of cluster prevalence [2], but they are lower than those derived from counting seizures during video-EEG monitoring [4,5,23], perhaps because such studies highlight people with intractable epilepsy, and during intentional medication withdrawal.

4.3. Factors associated with seizure clusters

Certain clinical factors associate with clusters. In the UK study of acute repetitive seizures [24], prevalence of such seizures was high (5.9/10,000) in those 0–4 years old and low (0.5/10,000) in those over 70 years. Age and sex were not associated with clusters [2], which is surprising because up to one-third of women with epilepsy are said to have catamenial exacerbation of seizures [25]. Our cohort had insufficient numbers of pediatric subjects to allow analysis of age as a factor in clustering. Those reporting clusters had significantly higher frequencies of nonclustered seizures than did those not reporting clusters, as has been previously reported [22]. Haut and associates [26] noted a significant association between clusters (defined as 3 seizures in 24 h) and remote symptomatic epilepsy, history of head trauma, extratemporal location, poor seizure control, and history of seizure-related hospitalizations. Clusters are also associated with increased risk of status epilepticus [27]. Status epilepticus occurred in 16 (44%) of 36 patients with clusters and in five (12.5%) of 40 patients without clusters ($p < 0.002$). People with clusters are more likely to have a higher seizure frequency, as our data confirmed, even when clusters are defined in terms of their baseline frequency. One interesting factor said to be associated with seizure clustering is the cycle of the moon [28].

Patients listed sleep issues, missing sleep, stress, menstruation, missed medications, illness, and alcohol as precipitants of clusters, but the observational nature of our data limits interpretation. The question arises as to whether one seizure makes a next seizure more likely ("seizures beget seizures"). Clustering could, however, result from an underlying factor, such as menstrual cycle, independent of the effect of one seizure on the next.

4.4. Interseizure intervals

Inpatient video-EEG recordings are the most accurate source of interseizure intervals but with important limitations. First, medications are often withdrawn, recording is short-term, and the environment is artificial. Second, there is no clear delineation between electrographic abnormalities and clinical seizures. Several reports [4,5,23] provide numbers of seizure pairs falling within specified intervals. A study with implanted subdural electrodes [23] observed clustering in 44% of their patients, but they did not report interseizure intervals, except to use a 4-hour window for defining clusters. In our study, interseizure time intervals on average declined with each subsequent pair of seizures. By the 4th-to-5th seizure, time separation had declined to 12 ± 14 min, raising the possibility of nondiscrete individual seizures. Our study found no natural grouping of times by which to define an interseizure interval that captures the large majority of seizures. Two-thirds of sequential seizures occurred within 6 h. Hypothetically, a medication with duration of action of 3 h, if used after the first seizure, would have been bioavailable at the time of 37% of subsequent seizures. Design of regimens to interrupt clusters of seizures [1] will need to consider drug pharmacokinetics and the possible need for repeat dosing.

5. Conclusion

Longitudinal data reported by over 28,000 patients using My Epilepsy Diary have provided the first overview of seizure clusters in a large community-based population. The data reported here describe cluster prevalence and frequency, distribution of interseizure time intervals, as well as the types of triggers commonly reported. Although limited by the self-reported and observational nature of the diary data, some general patterns emerge and can help to focus questions for future studies.

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Conflict of interest

RSF and JAC have no conflict of interest regarding the material in this study other than receipt of grant funding (to Stanford for RSF and to Irody for EB and JAC) for performance of the study. EB has, via Irody, Inc. partial ownership of My Epilepsy Diary.

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