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Seizure Clusters in Patients with Psychogenic Non-Epileptic Seizures

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SEIZURE CLUSTERS IN PATIENTS WITH
PSYCHOGENIC NON-EPILEPTIC SEIZURES

BY

GRAYSON LUDERMAN BAIRD

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

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IN

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OF
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ABSTRACT

There is a paucity of literature concerning seizure clusters for patients who suffer from psychogenic, non-epileptic seizures (PNES). The purpose of the present study is threefold. Manuscript one will explore how seizure clusters may be defined for patients with PNES using both statistical and traditional approaches of cluster identification. Manuscript two will examine seizure clusters as a primary outcome in patients receiving treatment for PNES. Cluster reduction is examined longitudinally using traditional and statistical definitions of seizure cluster for patients. Possible risk factors for clustering will also be examined along with clustering as a risk factor for poorer secondary outcomes. Last, research is presently lacking concerning how to describe and explain seizure clusters in patients with PNES. Manuscript three will explore how clusters have been defined so far in both the epilepsy and PNES literatures. In addition, theories as to why seizures cluster for patients with PNES will also be considered. The aim of these studies is to provide a foundation from which research and theory on seizure cluster definition and explanation may be advanced for patient with PNES.

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PREFACE

This dissertation is in manuscript format, in accordance with the required format for the medical journal *Epilepsia*, using a modified Vancouver style. The manuscript is split into three separate publications; the first two will be submitted together soon after feedback from the dissertation defense. The third will be submitted after the first two publications are (hopefully) accepted for publication.

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MANUSCRIPT – I

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Title: Identifying Seizure Clusters in Patients with Psychogenic Non-epileptic Seizures

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Seizure cluster, seizure clustering, PNES

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Summary

Objective: Explore how seizure clusters may be defined for those with psychogenic nonepileptic seizures (PNES), a topic for which there is a paucity of literature. The common threshold definition of cluster from the epilepsy literature is considered, along with a novel approach using statistical methods.

Methods: The sample was drawn from a multisite randomized clinical trial for PNES; seizure data are from patients' seizure dairies. Four cluster definitions were examined: 1) threshold definition, where ≥ 3 seizures in a day is considered a cluster, along with three statistical definitions, where ≥ 3 seizures in a day are considered a cluster if the observed number of seizures statistically exceeds what would be expected relative to a patient's: 2) average seizure rate prior to the trial, 3) observed seizure rate during the trial, 4) observed seizure rate for the previous seven days. Each statistical definition was also examined removing the ≥ 3 seizure requirement, called a "relative increase" event. Agreement, prevalence and rate of occurrence of clusters were examined for each definition and compared between definitions.

Results: Modest to good agreement was found between most definitions of cluster; the threshold definition identified the most clusters. Depending on definition, prevalence of clusters was 62-68% and for individuals who had clusters, they had them between 7-19% of the time, depending on the definition used. Prevalence was 91-97%, and rate of occurrence was 10.5-11.9% for relative increase events.

Significance: Although seizure clusters occur in clinical practice in those with PNES, there is a paucity of research in this area. The present study is the first empirical examination of clusters in a sample with PNES known to the authors and suggests clusters to be common in patients with PNES. More research is needed to identify if clusters are related to triggers and outcomes.

Key box

1. Seizure clusters occur in clinical practice in those with PNES, although there is a paucity of research on seizure clusters in the PNES literature.
2. The present study examines seizure clustering in a sample with PNES using patient seizure diaries from a clinical trial.
3. A common cluster definition from epilepsy literature was used to identify clusters, along with a novel approach using statistical methods.
4. Prevalence of clusters was 62-68% depending on cluster definition used, and occurrence rate of clusters was 7-19% depending on cluster definition.
5. Clusters seem to be common in patients with PNES, and more research is needed to identify if clusters are related to triggers and outcomes.

Identifying Seizure Clusters in Patients with Psychogenic Non-epileptic Seizures

Introduction

Psychogenic, non-epileptic seizures (PNES) are paroxysmal episodes that can resemble epileptic seizures but have psychological underpinnings ⁽¹⁾. Though often similar in manifestation, PNES are differentiated from epileptic seizures in that PNES are not associated with EEG epileptiform (i.e., patterns indicating epilepsy) correlates along with other clinical features of epilepsy ⁽¹⁾; thus, PNES are classified as a somatoform disorder of the conversion type (i.e., see Smith ⁽²⁾). Although dissimilar in etiology, both epileptic and psychogenic seizures can occur in clusters or bouts ^(3, 4). In particular, evidence indicates those who have epileptic seizure clusters have poorer outcomes relative to those who do not have clusters ⁽⁵⁾. Currently, there is a paucity of research concerning seizure clustering in those with PNES—including the operationalization of clusters. Research from the epilepsy literature ⁽⁴⁾ can be used to help inform the study and operationalization of seizure clusters for the population with PNES.

Seizure clusters are often defined as three or more seizures occurring within 24-hours in the epilepsy literature ⁽⁶⁻¹¹⁾. This definition was first introduced by Haut et al. ⁽¹²⁾, who observed that epileptic seizures occurring within 8 hours of each other were more likely to be concordant (i.e., same hemisphere foci) than discordant. Though the three or more threshold definition is clear and easy to implement in practice, the reasoning behind this cluster definition does not extend to PNES; what's more, this and other threshold-based definitions do not take into account a patient's relative seizure presentation. One consequence of using a threshold definition is patients who typically present with

repeated bouts of three or more seizures in a day will always be considered as having clusters, while relative increases in their seizure frequency will go unrealized.

Other studies have employed various statistical models to find evidence for epileptic seizure clustering. These models evaluate if a patient's seizure occurrence deviates from what would be expected due to randomness alone ⁽¹³⁻¹⁵⁾. One weakness with this approach is these statistical models only provide evidence for the presence of clustering, but seizure clusters themselves are not individually identified as events. Because a cluster itself is not identified as an event with these models, it is difficult to evaluate the improvement of clusters over time. In addition, these studies also used modeling approaches that assumed a patient's seizure rate remained constant. Though seizure frequency may remain stationary for some, this cannot be assumed for many patients, such as those receiving therapy or those who have been enrolled in a treatment trial and who may be experiencing a change in their baseline seizure frequency. For these patients, seizure frequency may be affected by a treatment effect, a placebo effect or a Hawthorne effect.

The present study will examine seizure clustering in patients diagnosed with PNES using four separate definitions of seizure cluster. The first definition will employ the standard count threshold approach of three or more seizures in 24 hours used in epilepsy. The remaining definitions, described shortly, will use Poisson modeling in identifying cluster events. These methods provide an alternative to threshold definitions by taking into account a patient's individual expected seizure frequency profile. Given that seizure clusters have been linked with deleterious outcomes in patients with epileptic seizures ⁽⁵⁾, the intent of the present study is to take a first step in providing researchers

and clinicians with multiple frameworks by which seizure clusters may be identified for patients with PNES. By providing clinicians with a means of identifying seizure clusters, subsequent studies can then examine clusters with outcomes specific for patients with PNES.

Methods

Sample. The sample is 34 patients diagnosed with PNES drawn from a multisite randomized clinical trial for PNES comparing psychotherapy, medication, and standard medical care. The arms include the antidepressant sertraline (MED), Cognitive Behavioral Therapy Informed Psychotherapy (CBT-ip), sertraline and CBT-ip (COMB), and Treatment as Usual/Standard Medical Care (TAU). During the trial, all patients recorded the daily number of seizures they experienced for a given day on a weekly calendar prospectively, starting at entry through the end of the trial. Clinicians reviewed and discussed the seizure logs with patients in the two CBT-ip arms at weekly appointments and those in the sertraline and TAU arms were reviewed and discussed in the bi-weekly appointments. In total, the logs of all patients were examined spanning between 11 to 32 weeks. Additional details about this sample can be found in LaFrance et al. ⁽¹⁶⁾.

Cluster definitions. Four seizure cluster identification definitions were examined in the present study. The first definition uses the count threshold approach, where three more seizures occurring in a day are considered a cluster ⁽⁴⁾. This definition was included because it is an established approach of defining a cluster in the epilepsy literature, thus making it a natural first step in examining clusters for those with PNES. The remaining three definitions provide an alternative approach of cluster identification by taking into

account a patient's typical seizure frequency (i.e., expected seizure rate). Each of the three definitions use a clinically informed and relevant reference of expected seizure count for determining if the number of seizures occurring in a given day can be considered a cluster event. Specifically, all three definitions use Poisson modeling, where three or more seizures in a given day is defined as a cluster when the number of seizures (statistically) exceeds what would be expected relative to a patient's:

- a. self-reported seizure count average at trial entry (subjective);
- b. observed seizure rate for the entire trial (observed);
- c. observed seizure rate for the 7 previous days of the day in question (seven).

The three or more seizures requirement was retained as a necessary but not sufficient condition of the statistical definitions; this was done to compare the threshold definition with the statistical definitions directly. For further comparison, the three statistical definitions were also examined removing the three or more seizure requirement (and will be referred to here as "relative increase" events instead of "cluster" events). Evidence for exceeding the number of expected seizures was defined at the $\alpha=0.05$ level for all statistical definitions.

It is important to clarify why each expected rate was selected as a reference. A patient's self-reported estimate of their average seizure count at trial entry was used as a natural and available reference of expected seizure rate, though this estimate may be inaccurate due to its subjective nature and recall bias. A patient's observed seizure rate for the entire trial is another natural reference of expected seizure rate, though this estimate can only be used after the trial has ended, thus not making it useful for clinical practice. Both the subjective and overall expected rates assume seizure frequency remains

constant over time; thus, neither reference can accommodate for a changing seizure rate due to the effects of treatment, placebo, Hawthorne (the effect from being observed or enrolled in a trial), or even regression towards the mean.

Instead of using a constant expected seizure rate, which is convenient but may not reflect clinical experience, another option is to use an expected rate on a week-by-week basis. The unit of a week or equivalently the prior 7 days can adjust for the possibility of a changing seizure rate while remaining constant if the patient's seizure rate is in fact static. In addition, the reference of the prior 7 days provides a natural reference for clinical practice because a patient's seizure logs are often reviewed on a week-by-week basis by a clinician.

Regardless of the expected seizure count reference used, all three statistical definitions follow the same form: when a patient experiences seizures in a day, the number of seizures observed for the day, s , is compared with one of the three expected rates, λ ; the cumulative distribution function (CDF) is given below:

$$1 - CDF(s, \lambda) = 1 - \left(e^{-\lambda} \sum_{i=0}^s \frac{\lambda^i}{i!} \right) \quad (\text{Equation 1})$$

where λ corresponds with either a) the patient's self-reported seizure rate; b) the total number of seizures each day divided by total days in the trial; c) the total number of seizures for the prior 7 days, divided by 7. Therefore, when a patient has s seizures in a given day and this number of seizures exceeds λ resulting with a p-value less than 0.05, then it is concluded that s seizures (statistically) exceeds what would be expected due to randomness alone, assuming the process is random.

It is important to clarify here that when p is less than 0.05, this is only evidence that the number of seizures for a given day is higher than what would be expected; concluding that this is evidence of a cluster is a(n) (definitional) extension of the threshold definition where three or more seizures constitutes a cluster, except here we include the patient's relative seizure frequency in making this conclusion. An α of 0.05 was chosen because the risk of incorrectly identifying a day's number of seizures as a cluster has low consequence, whereas missing a cluster is more important given their rarity. In addition, because we are only interested in evaluating increases in seizure counts, significance was determined only if the observed seizure count for the day was higher than expected.

Some patients typically present with several seizures a day while others may have relatively few seizures. Therefore, in addition to examining clustering overall, we will also examine cluster behavior in these two patient samples. Patients will be split into two groups based on their seizure frequency: those who reported having 21 or more seizures a week for at least 25% of the trial and those who did not. Although somewhat arbitrary, 25% of the trial was selected to differentiate between patients who may have the occasional high seizure frequency week from those who often have high seizure frequency weeks; 21 seizures a week was selected as it translates to a rate of three seizures a day, or one cluster a day, given the threshold definition.

Statistical methods. Agreement between cluster definitions was evaluated using Cohen's Kappa statistic (κ). In addition to agreement, the ratio of identified cluster events between definitions was also calculated. Rate of cluster occurrence for each definition was evaluated by calculating the percentage of days identified as being a cluster for each

patient and the mean and confidence intervals were calculated using a generalized linear model assuming a binomial distribution. Effect size was estimated by calculating the ratio between the observed and expected seizure counts for each definition. Overdispersion (i.e., large variability; when the variance is larger than the mean) was evaluated by calculating the ratio of the variance and mean (index of dispersion) for each statistical definition. Level of significance was established at 0.05 for all analyses and all interval estimates were calculated for 95% confidence. All analyses were conducted with SAS Software 9.2 (SAS Inc., Cary, NC) using the GLIMMIX, MEANS, and FREQ procedures.

Results

For clarity, each cluster definition will be referred to as the following: 1) “threshold” refers to the established three or more seizure a day definition; 2) “subjective” refers to a patient self-reported typical seizure rate at trial entry; 3) “overall” refers to a patient’s observed seizure rate for the trial; 4) prior “seven” refers to a patient’s seizure rate over the previous 7 days. To aide conceptualization, Figure 1 graphically illustrates all four definitions for a single patient during the trial.

Agreement between definitions. As indicated in Table 1, cluster event agreement was moderate to good between subjective, overall, and seven ⁽¹⁷⁾. Diminished agreement was found between threshold and the statistical definitions, achieving only fair agreement. Also revealed in Table 1 is threshold identified several more times clusters than statistical definitions. In its most extreme, the threshold identified 245 more cluster events than seven, an increase of 2.58.

Agreement was also assessed between each definition when removing the three or more seizure requirement. Agreement was diminished relative to the definitions requiring the three or more seizures. Good agreement was found between subjective, seven, and overall while agreement between threshold and statistical definitions was fair. Threshold identified 1.14 times more clusters than seven.

In addition, agreement was examined between the same definitions with and without the three or more seizure requirement (see cross diagonal in Table 1, darker grey). In general, when employing the three or more requirement, definitions identified roughly 50% fewer cluster than the same definitions without said requirement. By removing the three or more seizure requirement, cluster events consisting of only one or two seizures a day were identified 205, 193, and 195 times for subjective, overall, and seven definitions, respectively.

Prevalence of clustering in PNES. The prevalence of clustering varied by definition of cluster. In total, 68% (23/34) of patients were identified as having one or more cluster events at some point in the trial, as defined by threshold. Definitions overall and seven were slightly more conservative, identifying only 65% (22/34) of patients as having clusters while subjective identified 62% (21/34). Prevalence was also examined for all statistical definitions excluding the three or more seizure requirement. Definitions seven and subjective identified 91% (31/34) of patients as having one or more relative events at some point in the trial while definitions overall and subjective identified 94% (32/34). Prevalence was also examined between patients who had several seizures and those who did not. In total, 15% (5/34) of patients had 21 or more seizures a week for 25% of their time in the trial.

Rate of occurrence of cluster events. The rate of cluster events occurring in patients also varied by how a cluster was defined, as indicated in Table 2. Specifically, threshold identified individual patients as having cluster events on average 19% of the time while definitions seven, overall, and subjective identified clusters as happening 7.1%, 8.6% and 8.6% of the time, respectively.

Occurrence of relative increase events was also estimated. Definitions seven, overall and subjective occurred 10.5%, 11.4% and 11.9% of the time, only a slight increase relative to cluster occurrence.

In addition, cluster occurrence was examined between those identified as having several seizures and those who were not, as defined previously. As indicated in Table 2, large differences in occurrence were observed between two groups when using the clinical definition; however, differences between the two groups when using statistical definitions were relatively small and not significant, though overall and subjective definitions approached significance. No significant differences in relative increase event occurrence existed between those who had several seizures and those who did not.

Effect size. The median ratio between observed and expected seizures counts was examined as an estimate of effect size. When a cluster event was identified using a statistical definition, the observed seizure count was between 3.5-4 times higher than the expected count when using the three or more requirement and 4-4.6 times higher without said requirement.

Overdispersion and expected seizure count. Overdispersion occurs when the variance of the data is larger than the expected value. Because a Poisson model assumes that the variance and expected value are identical, when overdispersion is present, the

inference of the Poisson model is placed into question. Evidence for overdispersion was assessed by examining the median ratios of the variances and expected counts, where evidence of no overdispersion would result with a ratio of 1. For the overall definition, the median ratio was 1.7, thus indicating possible overdispersion. The observed variance and seven and subjective expected rates resulted in a ratio of 1.2 and 1.1, indicating little evidence of overdispersion. As an aside, the ratio between the subjective expected rate and the actual expected rate was found to be 1.4, indicating that the subjective expected rate was 40% higher (overestimated) than the actual rate.

Discussion

The present study examines seizure clustering in a sample with PNES using both an established definition of seizure cluster in epilepsy along with three alternative definitions that employ statistical methods. These statistical definitions provide an alternative to the established definition in that a patient's typical seizure frequency is used in determining if a patient had a cluster or not on a given day; statistical definitions are also a conceptual extension of the threshold definition in that the three or more seizures a day requirement is a necessary but not sufficient condition of cluster event identification. For comparison, these three statistical definitions were also examined without the 3 or more seizure requirement. This study also examined clustering between those who were identified as having several seizures a week with those who were not, as defined previously. These approaches bridge statistical and clinical methodology to inform patient care and clinical practice.

To the authors' knowledge, this is the first study examining seizure clusters in PNES using a prospectively collected longitudinal sample. Agreement, prevalence, and

rates of occurrence for clusters were analyzed across all definitions. Agreement between cluster definitions varied between moderate and very good, where lowest agreement was observed between the threshold definition and statistical definitions. In particular, the threshold definition identified several more clusters events than statistical definitions – 245 more events than the seven definition in particular. This is an especially relevant finding when considering the labor behind and complexity of detecting patterns of antecedents and outcomes associated with individual cluster events. That is, it may be easier to find correlates for specific triggers and outcomes of cluster events when there are fewer identified events and because these events are based not on simply hitting a threshold but also that they deviate from what would be anticipated. This is especially true for patients who typically have three or more seizures per day.

Agreement between threshold and statistical definitions for relative increase events were much lower compared with cluster events and ranged between fair and good, where the threshold definition identified only about 50 more events than the seven definition. Although the agreement between definitions was much lower than when retaining the three or more requirement, the differences in the actual number of events identified between definitions was not as great, thus indicating that the approaches are identifying drastically different events.

Estimates of prevalence between cluster definitions did not vary greatly, except when comparing the definitions using the three or more requirement with those without said requirement. For definitions using the three or more requirement, between 62% and 68% of patients enrolled in this clinical trial were identified as having seizure clusters at some point during the study; without the three or more seizure requirement, prevalence

was between 91% to 97%. These are the only known estimates of prevalence of PNES patients who cluster known to the authors. These findings suggest that seizure clustering is both not uncommon in patients with PNES and the prevalence may be higher than estimates found in patients with epilepsy. One study investigating clustering in epilepsy found 43% of patients had evidence of clusters using the threshold definition while 22% of patients had evidence of clustering using statistical modeling ⁽⁹⁾. Across multiple studies, prevalence of seizure clustering in epilepsy using either statistical modeling or threshold approaches is estimated between 18%-61% ⁽⁴⁾.

Estimates concerning the occurrence rate of clusters in PNES patients identified as having clusters varied greatly between threshold and statistical definitions; patients had clusters an average of 19% of the time when using the threshold definition compared with approximately 7%-9% when using statistical definitions. This difference becomes even more pronounced when comparing patients who typically present with several seizures each week versus those who do not: the former was estimated at having clusters 57% of the time and the latter 9% when using the threshold definition and approximately 9%-15% of the time for the former and approximately 11% for the latter when using statistical definitions. These results reveal that the average amount of time a patient is considered to be having clusters is very sensitive to the definition of cluster. Regardless of the definition used, the percentage of days patients are having seizure clusters is clearly nontrivial.

What is particularly noteworthy here is the estimated cluster occurrence rate is not significantly different between those who typically have several seizures and those who do not when using statistical definitions; this was also true for the rate of occurrence for

relative increase events. These results may be evidence for clustering as a phenomenon that has a common rate of occurrence that is not affected by a patient's typical seizure frequency.

In addition to the rate of clustering over time, magnitude of the increase in observed versus expected seizure counts was also examined (effect size). These results indicate that said magnitude varied somewhat depending on both statistical definition of cluster and whether a patient had been identified as having many seizures a week or not; however, in general, when a cluster event was identified using a statistical definition, the observed seizure count for a given day was approximately 3.5-5 times higher than the expected seizure count for that same day.

In general, only small differences were found between statistical definitions in terms of prevalence estimates and rates of occurrence, within but not between definitions with and without the three or more seizure requirement. Regardless of these small differences in prevalence and rate of occurrence, results from the agreement analyses reveal that the expected seizure count one uses does impact *which* days are considered clusters. What is not obvious from these findings is which expected seizure count reference should be used over the others references and when.

A patient's self-reported and subjective estimate of average seizure count at entry/baseline has the benefit of being both easy to implement and can be used immediately at the start of therapy. However, it has its drawbacks of being (by definition) subjective (and thus subject to recall bias) along with it cannot take into account for a patient's changing seizure rate over time. Therefore, cluster identification can be underestimated for those who reported an inflated seizure rate and overestimated for

those who reported a deflated seizure rate; change in seizure rate over time would only exacerbate these results.

On the other hand, the benefit of using the overall rate to identify clustering is it uses a patient's actual observed seizure rate. Like the subjective definition, it too cannot take into account a patient's changing seizure rate but unlike the subjective definition, this may be due to a regression towards the mean: any increases or decreases in seizure rate within a patient are balanced out. Consequently, cluster identification at the beginning of a trial or treatment window will therefore depend to some degree on seizure rates at the end of the trial and vice versa.

In addition, if a patient's seizure frequency throughout the trial is extremely variable, then the overall rate may not provide a good reference of a patient's expected seizure count, due to overdispersion; this may also be the case even if a patient's seizure frequency is only increasing or decreasing during the trial. What's more, an assumption of the Poisson test is that the reference (seizure) rate is stationary. Indeed, evidence of overdispersion was found for the overall definition but not for the seven definition. However, perhaps the greatest limitation with using the overall definition is it can only be used after a trial (or treatment period) has ended; thus, a clinician cannot use this definition to identify possible cluster events during the weekly sessions.

The remaining statistical definition, seven, is both easy to implement during therapy or a trial (i.e., one only needs to wait one week before using) and does take into account of a patient's changing seizure rate (thus reducing the risk of overdispersion). To calculate the expected rate, a clinician simply adds a patient's total number of seizures for the prior 7 days and divides by 7. The clinician then enters this rate along with the seizure

count of the day in question into one of the many Poisson calculators available on the Internet. The calculator will generate a p-value that reflects the probability of the observed seizure count (or greater) is due to random variation, assuming chance. One possible drawback of this approach is these cluster events may be increases due to a seasonality effect or other cyclical process. Checking for this possibility can require a great deal of data along with running a time series analysis, both of which may be prohibitive in clinical settings. Fortunately, if a clinician maintains a cluster log in parallel with a patient's seizure log, possible (simple) cyclical trends may in fact become evident without a formal time series analysis.

Limitations in this study include the following: there is a risk that patients may be unaware of the number and times of the seizure events they have in a day, thus compromising the accuracy of the self-report seizure logs; this risk may be even higher when patients have several seizures in a day. Because patients oftentimes did not record exact times of seizure onset during a day, our definition of three or more seizures is based on the recorded number of seizures in a day, which technically deviates from 24 hours definition often used ⁽⁴⁾. This limitation makes our threshold definition conservative, as it is possible for individual seizures to be counted multiple times for overlapping 24-hour intervals (thereby resulting in more clusters being identified).

An additional consideration is false positive rate. For all statistical definitions, alpha was established at the 0.05 level. This level was chosen because it is familiar to medicine; a smaller alpha was not used as the risk of incorrectly identifying a group of seizures as a cluster has low consequence while not missing a cluster was more important (given their rarity).

A final limitation of this study is the concept of a cluster itself. In this study, the three or more seizure definition of cluster was used alone as well as a necessary but not sufficient condition of cluster identification for statistical definitions. In so doing, the threshold definition and statistical definitions all preclude cluster identification in those patients who do not have more than two seizures at any point. However, the three or more requirement is used only out of convenience and tradition, as there is no way of knowing if multiple seizures in a given day really constitute a cluster; likewise, it is easily justifiable that any seizure following a single seizure may be considered a cluster.

For instance, when the three or more seizure requirement was removed from the statistical definitions, relative increase events were identified when any number of seizures occurred in a day that were significantly higher than expected, including only a single seizure event. By removing the three or more seizure requirement, one could simply consider these events “relative increases” instead of clusters per se. The benefit of this approach is clinicians could identify days when a patient has had a higher number of seizures than would be expected, regardless of the actual number of seizures said patient has had.

The importance of this paper is threefold. First, the present study provides both the research and clinical communities with multiple frameworks by which seizure clusters may be identified as events. Second, with these frameworks, estimates of prevalence and rate of occurrence for clusters are now available for the population with PNES. Third, the results from this study reveal the differences between identifying a cluster as an event due to a certain number of seizures occurring versus identifying a

cluster as an event because it is relatively unexpected. This distinction can be important in both clinical practice and research.

For example, those who typically have 3 or more seizures a day will be considered to typically present with clusters when using the threshold definition ⁽⁴⁾ while this would be an impossibility using statistical approaches, where cluster events are, by definition, not typical. The distinction between a cluster as a typical event versus an atypical event becomes important when trying to identify possible triggers and outcomes associated with clusters ^(9, 18). Specifically, it would be difficult to identify specific triggers and outcomes associated with cluster events in patients who typically present with clusters; the opposite would be true when cluster events stand apart from typical seizure events. Thus, statistical definitions can aid clinicians and researchers in identifying triggers and outcomes associated with cluster events while the threshold approach may not be able to do this, especially in patients who typically present with several seizures.

In summary, although seizure clustering is known by clinicians to exist in patients with PNES, and research from epilepsy indicates that epileptic clusters are associated with poorer outcomes, there is little or no research being conducted on seizure clustering for the PNES population. This study has taken a first step in providing researchers and clinicians with a means of identifying cluster events for patients with PNES.

Now that cluster events can be identified, clinicians and researchers can examine cluster events as outcomes of interest, whether to track an individual patient's cluster trajectory in therapy or an entire treatment arm in a clinical trial. The ability to identify cluster events also enables clinicians and researchers the ability to identify specific

triggers and outcomes associated with these cluster events. With the ability to distinguish between patients who cluster with those who do not, demographic and other patient characteristics can be used to assess if risk factors exist for clustering in the population with PNES. Moreover, in addition to having more frequent seizures in a day, other consequences of clustering, such as increased depression or decreased quality of life relative to those who do not cluster, may also be assessed, thus enabling researchers to identify clustering as a possible risk factor for poorer outcomes in patients with PNES. These and other efforts to better understand seizure clustering for patients with PNES have potential to inform clinical practice and improve patient care.

Table 1. Agreement between definitions: Kappa and ratios

3 or more seizure	Threshold	Subjective	Overall	Seven	Events
Threshold	1.0	1.34	1.19	2.58	400
Subjective	.57	1.0	.93	1.10	299
Overall	.60	.81	1.0	1.12	336
Seven	.53	.69	.78	1.0	155
Any seizures	Threshold	Subjective	Overall	Seven	
Threshold	NA	1.11	1.11	1.14	400
Subjective	.38	.48	1.0	1.01	360
Overall	.42	.70	.51	.96	360
Seven	.34	.61	.70	.44	351

Areas in grey are ratios, where the numerator is the row definition

Areas in white are Kappa statistics

Table 2. Rate of Cluster Event Occurrence

	All		Patients with several seizures				Patients without several seizures			
	Estimate	95% CI	Estimate	95% CI	Min	Max	Estimate	95% CI	Min	Max
<i>Cluster events</i>										
*Threshold	19.26	[10.96, 31.6]	57.00	[34.00, 78.00]	18.80	92.47	9.00	[06.00, 12.00]	0.97	19.61
Seven	7.07	[5.54, 8.98]	09.29	[05.71, 14.76]	2.33	16.09	06.42	[04.95, 08.29]	1.04	11.58
Overall	8.55	[6.56, 11.07]	11.97	[08.54, 16.54]	7.95	18.09	07.79	[05.67, 10.61]	0.97	18.05
Subjective	8.63	[5.71, 12.84]	14.91	[06.98, 29.04]	1.08	35.23	6.67	[04.66, 09.46]	1.19	16.67
<i>Relative increase events</i>										
Seven	10.52	[8.78, 12.56]	09.29	[05.77, 14.61]	2.33	16.09	10.74	[08.84, 12.99]	0.85	18.68
Overall	11.38	[9.64, 13.39]	11.97	[08.60, 16.43]	7.95	18.09	11.30	[09.38, 13.54]	0.80	21.43
Subjective	11.87	[8.55, 16.25]	14.91	[07.10, 28.64]	1.08	35.23	11.29	[07.83, 16.0]	0.80	39.26

Estimates are the mean percent of days (out of 100%) when clusters were observed

Estimates and 95% confidence intervals are listed for those with and without several seizures per week and all patients

^{*}p<.05

Figure 1

All four seizure cluster definitions for a single patient over the span of the trial.

1. X-Axes are "Time" in days
2. Y Axes are "Seizure counts"
3. Hollow circles are seizure counts
4. Filled circles are identified clusters
5. Grey areas denote statistical cutoff for a cluster being identified
6. Black line denotes the 3 or more threshold
7. Expected counts are dark grey lines
8. All using 3 or more seizure requirement
9. Subjective and overall have similar expected seizure counts (grey lines)
10. Note: This patient was selected because both their subjective and overall rates were approximately 3 seizures per day, thus providing a direct comparison with the threshold definition.
11. Note that the threshold definition identifies the most cluster events and the seven definition the fewest.

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Title: Cluster Reduction in Patients in a Pilot Treatment Trial for Psychogenic Non-epileptic Seizures

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Summary

Objective: Examine seizure clusters as a primary outcome in patients receiving treatment for PNES. Cluster reduction is examined longitudinally using traditional and statistical definitions of seizure cluster for patients. Possible risk factors for clustering will be examined along with clustering as a risk factor for poorer secondary outcomes.

Methods: Participants were from a pilot randomized treatment trial for PNES where they received CBT-ip, sertraline, combination therapy, or treatment as usual; seizure data are from patients' seizure dairies. Definitions of seizure cluster as described in Baird et al.⁽¹⁾ were used. Cluster events were modeled as a primary outcome using generalized estimating equations, where clusters were nested within patients. In addition, several demographic and clinical factors were examined as predictors of whether a patient had clusters or not using a Fisher Exact Test; patients with and without clusters were compared on several secondary outcomes using a generalized linear model.

Results: Cluster reduction was observed for those receiving CBT-ip or combination treatment using all definitions of daily clusters and weekly clusters. No risk factors of clustering were observed. Those who were identified as having clusters during the trial had poorer secondary outcomes on several measures at baseline relative to those who were not identified as having clusters.

Significance: This is the first study known to the authors to not only examined seizure clusters as a primary outcome for those with PNES, but also the first study to suggest that

CBT-ip and combination therapy may be effective in reducing the frequency of clusters.

In addition, this is the first study to indicate that those who have clusters may have poorer secondary outcomes relative to those who do not. These results have the potential to inform clinical practice for PNES while also advancing the research methodology of seizure clusters for both PNES and epilepsy.

Key box

1. Despite seizure clusters occurring in clinical practice, there is a paucity of research examining clusters as an outcome of interest for PNES.
2. The present study examines seizure clusters as a primary outcome of interest from a four-arm treatment trial for PNES.
3. Both traditional and statistical definitions of clusters as outline in Baird et al.⁽¹⁾ were used to identify clusters during the duration of the trial.
4. Daily cluster reduction was observed with all definitions of cluster for those receiving CBT-ip or combination therapy.
5. Results from this study may help to inform clinical practice for PNES and advance research on seizure clusters in general for both PNES and epilepsy.

Introduction

It is estimated that roughly 2-33 per 100,000 people in the general population ⁽²⁾ and up to 20% of those with epilepsy suffer from psychogenic nonepileptic seizures (PNES) ⁽³⁾. Despite being as prevalent as MS and Parkinson's ⁽⁴⁾, to date, relatively few randomized controlled trials (RCTs) have been conducted examining treatment for PNES. An early single-arm cognitive behavioral therapy (CBT) trial demonstrated significant seizure frequency reduction over 12 weeks ⁽⁵⁾ while a subsequent two-arm RCT found those in the CBT arm reported greater reduction in seizure frequency relative to those receiving standard medical care (SMC) ⁽⁶⁾. Another two-arm RCT found those receiving sertraline reported a significant decrease in seizure frequency, while those in the placebo arm did not ⁽⁷⁾. These same researchers also conducted a single arm trial which found patients receiving cognitive behavioral informed psychotherapy (CBT-ip) experienced a reduction in seizures, improvement with comorbidities, and increased functioning ⁽⁸⁾. Recently, a four-arm RCT examining CBT-ip, CBT-ip+ sertraline, sertraline medication (MED), and treatment as usual (TAU) found that those receiving CBT-ip or CBT-ip + sertraline experienced a significant reduction in seizure frequency, while the reduction in those receiving sertraline alone only approached significance; no significant reduction in seizures or comorbidities was found in those receiving TAU ⁽⁹⁾.

What is common in all five trials is the primary outcome of interest was seizure frequency, though many important secondary outcomes, such as quality of life, depression, etc., were also examined. Focus on seizure frequency as the primary outcome of interest is understandable, given that seizures are the defining feature of a

PNES diagnosis along with seizure events being a major source of both dysfunction and subjective distress for patients. Given that individual seizure events can be both debilitating and distressing, it follows that when seizure events are more frequent than usual, their impact may be more disruptive than usual. Within the epilepsy literature, Haut has examined the phenomenon of seizure clustering, whereby multiple seizure events happening within a specified time interval are considered a cluster⁽¹⁰⁾. Research on seizure clusters indicates that clustering is associated with poorer outcomes in the population with epilepsy⁽¹¹⁾.

Though seizure clustering in patients with PNES is both acknowledged in the literature⁽¹²⁾ and known to clinicians, presently, only one study known to the authors has examined clustering in patients with PNES⁽¹⁾. That study examined seizure clusters as events using four different definitions of cluster along with estimating prevalence of clustering and frequency of clusters in the population with PNES. Currently, there is no research known to the authors examining cluster events as a primary outcome of interest for a RCT treatment trial for PNES. Likewise, the authors are unaware of research examining both risk factors associated with clustering and clusters as risk factors for poorer outcomes for patients with PNES.

The present study examines cluster events as a primary outcome of interest in patients enrolled in a four-arm RCT for PNES. In addition, this study will also examine possible risk factors for clustering along with examining clustering as a risk factor for poorer secondary outcomes. We hypothesize that arms receiving a psychotherapy and medication treatment will experience a reduction in cluster frequency, while the TAU arm will experience no significant reduction in cluster frequency. In addition, we

hypothesized that those who are identified as having clusters also will have poorer outcomes relative to those who do not have clusters.

Methods

Sample and Design. The sample and design for this study is from a pilot randomized clinical trial with four treatment arms: cognitive behavioral informed psychotherapy (CBT-ip), sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and TAU. In total, 34 patients were followed anywhere between 11 and 34 weeks, where patients prospectively recorded their daily seizures on calendars for the duration of the trial. These logs were reviewed and discussed by clinicians with patients in the two CBT-ip containing arms at weekly appointments and at bi-weekly appointments for patients in the sertraline and TAU arms. Further details concerning this trial and its sample can be found in the study article ⁽⁹⁾.

Cluster identification. Cluster events were identified using the four definitions examined previously (see Baird et al. ⁽¹⁾). The definitions include the traditional threshold approach, which defines a cluster as three or more seizures in a given day, along with three alternative definitions that use Poisson modeling. For all three statistical definitions, a cluster event was identified when three or more seizures for a given day statistically exceeded the number of expected seizures. Each statistical definition differed in how the expected seizure frequency was calculated. These expected seizure rates were:

- a. subjective average seizure occurrence at trial entry (i.e., “subjective”);
- b. observed seizure rate for the entire trial (i.e., “overall”);
- c. observed seizure rate for the previous 7 days of the day in question (i.e., “seven”).

A full treatment as to why each expected seizure rate was considered can be found in ⁽¹⁾.

As with Baird et al. ⁽¹⁾, statistical definitions use the three or more seizures requirement as a necessary but not sufficient condition of cluster identification – thus making these statistical definitions conceptual extensions of the traditional threshold approach. For comparison, statistical definitions were also examined removing the three or more seizure requirement, where any number of seizures in a given day was considered a “relative increase” when the number of seizures observed statistically exceeded the expected number of seizures for the given day. Evidence that the observed seizure count exceeded the expected count was established when $p < 0.05$.

As in Baird et al. ⁽¹⁾ for clarity, the three or more seizure definition will be referred to as “threshold”; statistical definitions of cluster will be distinguished by their respective expected seizure rate references: thus statistical definitions will be referred to as “subjective”, “overall”, and “seven”. In addition, statistical definitions without the three or more seizure requirement will be referred to as “relative increase” events instead of “cluster” events.

Risk factors. Several patient characteristics, such as demographics, medical history, comorbidities, neurological results, and current medications, were examined as possible risk factors for clustering.

Secondary outcomes. The following secondary measures were used to assess other aspects of patient functioning: the Beck Depression Inventory–II (BDI), Beck Anxiety Inventory (BAI), Barratt Impulsiveness Scale (BIS), Davidson Trauma Scale (DTS), Dissociative Experiences Scale (DES), Symptom Checklist 90 (SCL), Quality of Life in Epilepsy Inventory 31 (QoL), QOL Burden to Family Scale, Expectations Scale, Global Assessment of Functioning (GAF), Hamilton Depression Rating Scale (HAM-D),

Oxford Handicap Scale (OHS), Clinical Global Impressions–Improvement scale (CGI-Imp), and Clinical Global Impressions – Severity Scale (CGI-Sev). Other outcomes that were examined include utilization and functioning variables: emergency room (ER) visits, urgent physician (MD) visits, hospital admission, disability status, driving status, and unemployment status. Because this trial was not powered to detect differences between those who clustered and those who did not within treatment arm, potential impact of clustering on secondary measures could only be assessed at baseline.

Statistical Methods. All analyses were conducted using SAS 9.2 (SAS Software Inc, Cary, NC). Cluster events and relative increase events were examined over time for each treatment arm using each of the four cluster definitions as previously described. Daily cluster events were modeled using generalized estimating equations (GEE), where cluster events were nested within patient; a Bernoulli distribution was assumed because presence or absence of cluster was being modeled. In addition, total weekly seizures were modeled using GEE, where weekly cluster events were nested within patient; a Poisson distribution was assumed because count of weekly clusters was being modeled. Differences in demographics and possible risk factors for clustering were examined using Fisher’s Exact test or Pearson Chi Square tests with Cramer’s V for categorical data and Wilcoxon tests for continuous data. Secondary outcomes were evaluated using generalized linear modeling assuming a binomial distribution or Poisson distribution. PROC GLIMMIX was used for all modeling and PROC FREQ and NPAR1WAY were used for testing differences between risk factors. Overdispersion (extreme variability) was evaluated to examine if using a Poisson distribution for statistical cluster definitions was appropriate; this was done by taking the median value of the ratio of variance and the

expected value, where a large ratio over 1.0 is evidence of overdispersion. Alpha was established at the 0.05 level for all statistical analyses and all interval estimates were calculated for 95% confidence.

Results

Prevalence of Clusters. When using the definition “threshold”, 68% (23/34) patients were identified as having cluster events, though clusters were not equally occurring across treatment arms: CBT-ip 55.6% (5/9), COMB 55.6 (5/9), MED 88.9% (8/9), TAU 71.4% (5/7). When using the definition, “seven,” 65% (22/34) were identified as having a cluster, where 45.4% (4/9) of those receiving CBT-ip were identified as having cluster events. When using the definition, “subjective”, 62% (21/34) patients were identified as having cluster events, where 57.1% (4/7) of patients in TAU had cluster events. As with the “seven” definition, 65% (22/34) were identified as having cluster events when using the “overall” definition, though here, only 77.8% (7/9) of patients in the MED arm had cluster events. For brevity, the “threshold” definition of cluster will be used when examining risk factors and outcome differences between those who cluster and those who do not. The “threshold” definition was selected as it identified the most clusters and was almost identical to the “seven” and “overall” definitions, save for one patient each.

Risk factors of clusters. Demographic factors along with medical history, medications, comorbidities and neurological results were examined between those who cluster and who did not cluster. As revealed in Table 1, no statistically significant differences were found for risk factors between those who cluster and those who do not cluster.

Daily cluster events. As indicated in Table 2, daily cluster events significantly decreased for the CBT-ip and COMB arms across almost all definitions of cluster. However, no significant cluster reduction was observed for the MED and TAU arms for any definition of cluster. The results for relative increase events mirror those of cluster events: CBT-ip and COMB arms significantly decreased across many definitions, while MED and TAU do not.

Total weekly cluster events. As indicated in Table 3 and Figures 1 and 2, cluster events significantly decreased for those in the COMB arm for all definitions, while CBT-ip significantly reduced when using the “threshold”, “seven”, and “overall” definitions. Specifically, weekly cluster events reduced between 8-9% for the CBT-ip arm and 7-10% for COMB arm, depending on the definition used. No significant reduction in cluster events was observed in either MED or TAU arms for any definition. Of note, when using the “seven” definition, cluster events actually increased for TAU, though not significantly. In addition, relative increase events significantly reduced in the CBT-ip arm for all definitions with the exception of “subjective”, while the COMB arm significantly reduced for all definitions.

Secondary outcomes. As shown in Table 4, several secondary outcomes at baseline were significantly worse for those subsequently identified as having seizure clusters relative to those who were not. Specifically, those found to have clusters scored higher (worse) on the BDI, HAM-D, BIS, DES, and CGI-severity, along with scoring lower (worse) on QoL, compared with patients who were not identified as having seizure clusters. In addition, those identified as having clusters scored higher (worse) on the SCL and DTS, compared with those not identified as having clusters, though these differences

only approached significance. No significant differences were found between those who cluster and those who do not for several other outcomes, including BAI, GAF, OHS, CGI-improvement, ER, MD, and hospital admissions.

Overdispersion. Overdispersion appears to be a possible problem for the “overall” definition estimate only, and perhaps for COMB treatment, especially with subjective and overall definitions, as evidenced by the dispersion index values greatly over 1 (see Table 5). Thus, cluster identification using these definitions may not be appropriate given that the Poisson distribution assumes the mean and variance are the same value. As a consequence, any results stemming from these definitions should be interpreted with caution. In addition, the ratio between the subjective expected rate and the actual expected rate indicates that the subjective ratio overestimated seizure frequency between 10%-80% depending on the treatment arm (see Table 6).

Discussion

The present study examined seizure clusters as a novel primary outcome of interest in a RCT designed for treating patients with PNES. In addition, potential risk factors for clustering in patients were also examined. Last, secondary outcomes were examined between those who cluster and those who did not as a means of identifying clusters as possible risk factors for poorer outcomes.

As previously reported in Baird et al. ⁽¹⁾, depending on the cluster definition, prevalence of patients having cluster events was found to be between 62%-68%, while the prevalence of patients having relative increase events was between 92%-94%. No potential risk factors for clustering were found with patient demographic characteristics, medical history, comorbidities, medications, or biometrics. These findings are not

necessarily surprising, given the small sample size of the study and the small proportion of those who were not found to cluster in particular (n=11).

Several positive results were found for both daily and total weekly cluster events. Significant reductions in daily and weekly cluster events were observed for both CBT-ip and CBT-ip/sertraline treatment arms when using most definitions of cluster events and relative increase events. These findings are especially promising, as they indicate that these psychotherapeutic treatment modalities may be effective for the population with PNES in reducing not only seizure events, as found in ⁽⁹⁾, but also cluster events and relative increase events.

Moreover, the consistency in outcomes among the definitions, especially threshold and seven, also strengthens the evidence that patients in the two CBT-ip treatment arms actually experienced a decrease in cluster events and relative increase events. Interestingly, the similarity in outcomes across the four definitions also places into question the utility of using statistical approaches of cluster identification. That is, if the outcomes are similar, then what is the benefit of using a statistical approach over the traditional threshold approach?

To answer this question, it is important to first note that a reduction in cluster events for the CBT-ip and CBT-ip/Sertraline arms when using the threshold definition is not entirely unexpected. LaFrance et al. ⁽⁹⁾ observed a significant reduction in seizure frequency in both CBT-ip and CBT-ip/Sertraline arms. Because clusters are a pure function of seizure frequency when using the threshold approach, it follows that a reduction in seizure frequency would also lead to a reduction in clusters, though this outcome is not guaranteed. Specifically, patients may have experienced a decrease in

seizure counts but remained above the three seizure threshold –thus a reduction in seizures would not lead to a reduction in clusters (as defined by the threshold approach).

On the other hand, statistical definitions are far less dependent on seizure frequency. Because the three or more seizure threshold is only a necessary but not sufficient condition of a cluster for statistical definitions, statistical clusters are therefore a function of both the three or more seizure threshold and if the number of seizures in a day statistically exceeds what would be expected. Unlike the threshold definition, cluster reduction can be realized even for days in which three or more seizures occur. In addition, the seven definition is even less affected by a patient's seizure frequency as this definition uses only a patient's immediate seizure rate in determining if a given day exceeds the number of seizures expected, instead of a patient's static perceived or actual overall seizure frequency rate, as with the subjective and overall definitions. By removing the three or more seizure requirement defining a cluster, relative increase events are even less affected by seizure frequency, as a relative increase event can be any frequency of seizures that exceeds what is expected.

Given the aforementioned differences between definitions, it is not surprising that large differences are observed in both the number and concordance of events identified between the threshold definition, the statistical definitions, and relative increase events ⁽¹⁾. What is even more remarkable is despite identifying fewer cluster events, statistical definitions indicate significant cluster reduction just as the threshold definition. As discussed in detail by Baird et al. ⁽¹⁾, statistical definitions may be better at identifying specific triggers and direct outcomes associated with cluster events (or relative increase events) because these approaches identify days in which seizure frequency is worse than

expected. On the other hand, the threshold definition is unable to identify days in which seizure frequency is worse than expected because cluster events are identified using an all or nothing threshold (instead of a threshold relative to a patient's typical seizure frequency). Moreover, statistical definitions, especially seven, identify far fewer events than the threshold definition, thus making it easier to detect possible said triggers and outcomes.

Therefore, there are several reasons why statistical approaches have utility over the threshold definition. First, the seven definition is not bound entirely by seizure frequency, nor is cluster reduction only a function of having fewer than three seizures. As such, when using the seven definition, greater confidence can be ascribed to observed reductions in cluster events because said reductions are not simply a product of decreasing seizure counts falling under some arbitrary threshold. In addition, statistical definitions lend themselves well to identifying possible triggers and outcomes associated with days in which seizure frequency is worse than expected; *although this results in fewer cluster events being identified, this does not seem to come at the cost of evaluating cluster reduction*, given the consistency in cluster reduction outcomes across all definitions.

Although these results lend support that CBT-ip and COMB treatments are effective in reducing cluster frequency, it is important to note that the trial was not powered to detect differences between arms. Therefore, these results are not evidence that CBT-ip and COMB are better than the other treatment arms, but rather that significant improvement was observed in these arms but not the others. Thus, a larger sample is needed to both confirm these findings as well as be able to detect between group

differences. Aside from being underpowered to make between-group comparisons, another limitation of the study results is cluster events were identified after the trial; thus, it was impossible to equally assign those who cluster with those who do not across the treatment arms. As such, imbalance exists between the treatment arms in terms of the number of patients within each arm who cluster.

Another weakness inherent in this study analysis is type I error. Specifically, there is a type I error (rejecting the null when the null is true) associated with each cluster identified; for statistical definitions, the type I error rate is controlled at the 0.05 level. However, there is also a type I error associated with the modeling of cluster reduction. Because of the small sample size and the exploratory nature of this study, significance for cluster reduction was also set at the 0.05 level. However, the error rate from cluster identification does affect the results of the cluster reduction. A possible correction for this problem would be to simply decrease the size of alpha so to ensure that the results are not an artifact of a compounding type I error. Therefore, a well-powered treatment trial is needed using a design stratifying those who cluster and those who do not, so that the relative effects of each treatment arm may be estimated, not only for seizure frequency but also for cluster frequency.

Several differences were observed between those identified as having cluster events and those who did not. Those who have clusters, not surprisingly, showed worse symptom and functioning mean scores. Specifically, those who were not identified as having clusters scored on average in the “mild” range of depression while those identified as having clusters scored in the “moderate” range of depression on both the BDI-II and the HAM-D. In addition, the average QoLIE-31 score for those who had clusters was

significantly lower compared with those who did not have clusters. Interestingly, these results differ from those reported for the epilepsy population, where no difference was found between those who cluster and those who do not on the BDI-II and QoLIE-89 ⁽¹¹⁾.

In addition, those identified as having clusters also had poorer average outcomes on several measures relative to those not identified as having clusters, including higher DES scores, indicating more dissociation from self, higher BIS scores, indicating more impulsivity, and higher CGI-severity scores, where those having clusters were closer to being markedly ill while those without clusters were closer to being only moderately ill. Those with clusters also had higher DTS scores compared with those who did not have clusters, indicating greater risk for PTSD, though this difference only approached significance. However, no significant differences between those with and without clusters were found on many measures, including the BAI (anxiety), GAF (global functioning), OHS (handicap), and CGI-improvement. Although Haut ⁽¹¹⁾ found patients with clusters had significantly more seizure-related hospitalizations than those without clusters for patients with epilepsy, no such differences were found for ER visits, urgent visits with the physicians, and hospital visits in general in this PNES sample.

Though these results may be evidence for seizure clusters having deleterious effects on secondary outcomes, this conclusion may be premature and should be met with some caution. As mentioned previously, clusters could only be identified after the trial's completion, thus making it impossible to randomize those with and without clusters into treatment arms. This presents potential problems: the possible treatment effect on secondary measures between those with and without clusters could not be assessed therefore, secondary measures collected at the trial's end contain the possible effects of

clustering and effects of treatment. Thus, only the secondary measures collected at entry could be used as these measures contained no possible treatment effect, though these measures were collected before clusters could be identified.

The weakness here is obvious: the effects of clustering cannot be inferred after clusters have been identified. Therefore, we are assuming that those identified as having clusters during the trial also had them prior to the trial. We do not know, however, if those identified as not having clusters were not having them before the trial. Both may have had clusters pre-trial, but because of the constraints of the study, this is the only methodology to go about estimating the possible effects of clusters on secondary measures. Therefore, again, a well-powered randomized control trial stratifying for clusters could assess both the effects of clustering on secondary measures and the treatment effects on secondary measures between those who cluster and those who do not.

In summary, the results from this study are very promising regarding clusters as a novel outcome in PNES. Using most definitions of cluster identification, CBT-ip and CBT-ip/sertraline treatment appears to reduce cluster events over time for patients with PNES; there was also some evidence that clusters may reduce in those receiving sertraline alone. Although no significant demographic or risk factors were identified for those having clusters, several secondary measures indicate that those who have clustering may be a risk for poorer secondary outcomes relative to those without clustering. The results from this study call for additional research in the area of seizure clustering for patients with PNES.

Table 1. Risk Factors of Those Who Cluster Relative to Those Who do not

	Clusters (n=23)		Not (n=11)		Effect	P
Demographics						
Gender (F)	91.3%	21/23	90.9%	10/11	0.00	0.99
Race						
White		20/23		3/10		
Black		2/23		0/10		
Age, y	36.0	(20-56)	40.0	(21-57)		.5594^
Age onset of PNES, y	33.0	(13-54)	39.0	(21-57)		.8538^
Time Onset to Treatment, y	2.6	(0.1-14.9)	2.9	(.5-12.7)		.6321^
Education, y	14	(10-22)	16	(12-24)		.3496^
Medical History						
Past Substance Abuse	43.5%	10/23	45.5%	5/11	-.02	0.9135
Substance Abuse	43.5%	10/23	36.4%	4/11	0.07	0.99
Exposure to Seizures in Others	56.5%	13/23	54.5%	6/11	-0.01	0.99
Biological Family History						
Seizures	30.4%	7/23	27.3%	3/11	0.03	0.99
History of Headache	82.6%	19/23	81.8%	9/11	0.01	0.99
History of Migraine	56.5%	13/23	63.6%	7/11	-0.07	0.99*
History of Psychotherapy	56.5%	13/23	63.6%	7/11	-0.07	0.99*
Sexual Trauma	60.9%	14/23	54.5%	6/11	0.06	0.7259
Emotional Trauma	39.1%	9/23	45.5%	5/11	-0.06	0.7259
Verbal Trauma	39.1%	9/23	54.5%	6/11	0.14	0.3971
Physical Trauma	56.5%	13/23	54.5%	6/11	0.02	0.9135
Medications						
Current antidepressants	65.2%	15/23	63.6%	7/11	0.02	0.99*
Current antipsychotics	8.7%	2/23	27.3%	3/11	-0.25	0.3
Current benzodiazepines	52.2%	12/23	63.6%	7/11	-0.11	0.7152
Current Optimized Antidepressant	34.8%	8/23	18.2%	2/11	0.17	0.4375
Currently on Antiepileptic Med	47.8%	11/23	81.8%	9/11	-0.32	0.0764
Currently on Psychotropic Med	87.0%	20/23	90.9%	10/11	-0.06	0.99*
Comorbidity						
Attention Deficit Disorder	13.0%	3/23	9.1%	1/11	0.06	0.99*
Anxiety Disorder	73.9%	17/23	63.6%	7/11	0.11	0.6915
Personality Disorder Diagnosis	65.2%	15/23	36.4%	4/11	0.27	0.1512
Generalized Anxiety Disorder	60.9%	14/23	45.5%	5/11	0.14	0.3971
Post Traumatic Stress Disorder	39.1%	9/23	36.4%	4/11	0.03	0.99*
Panic Disorder	13.0%	3/23	9.1%	1/11	0.06	0.99*
Somatoform Disorder W/O Conversion	21.7%	5/23	9.1%	1/11	0.16	0.638*
Traumatic Brain Injury	63.6%	14/22	63.6%	7/11	0.00	0.99*
Mood Disorder	60.9%	14/23	63.6%	7/11	-0.03	0.99*
Neuro-metrics						
Ambulatory EEG	43.5%	10/23	60.0%	6/10	-0.15	0.4646
Routine EEG	69.6%	16/23	81.8%	9/11	-.22	0.3820
Abnormal finding	31.8%	7/22	70.0%	7/10	0.34	0.1756
MRI of the brain	78.3%	18/23	90.0%	9/10	-0.14	0.640*

All analyses were conducted using Pearson Chi Square Test of independence, unless otherwise specified;* Fisher Exact Test (two tailed); used when one or more cells had a count fewer than 5.

^ Independent samples t-test and 95% confidence intervals; Effect size used was Crame

Table 2. Daily Cluster Events, by Treatment Arm and Definition

Definitions	Arm	Cluster Events			Relative Increase Events		
		Change	95% CI	P	Change	95% CI	P
Threshold	CBT-ip	0.497*	[0.4947, 0.4995]	0.0086			
	COMB	0.497*	[0.4950, 0.4985]	0.0002			
	MED	0.500	[0.4981, 0.5011]	0.3029			
	TAU	0.497	[0.4890, 0.5050]	0.2341			
Subjective	CBT-ip	0.498	[0.4953, 0.5011]	0.1099	0.498	[0.4947, 0.5014]	0.1219
	COMB	0.497*	[0.4945, 0.4988]	0.0010	0.498*	[0.4954, 0.4999]	0.0199
	MED	0.500	[0.4971, 0.5025]	0.4448	0.501	[0.4974, 0.5040]	0.3431
	TAU	0.500	[0.4908, 0.5084]	0.4629	0.499	[0.4929, 0.5048]	0.3496
Overall	CBT-ip	0.497*	[0.4946, 0.4994]	0.007	0.497*	[0.4937, 0.4997]	0.0145
	COMB	0.497*	[0.4951, 0.4988]	0.0006	0.496*	[0.4937, 0.4987]	0.0019
	MED	0.501	[0.4966, 0.5046]	0.3863	0.499	[0.4953, 0.5028]	0.3020
	TAU	0.497	[0.4891, 0.5051]	0.2393	0.497	[0.4901, 0.5036]	0.1779
Seven	CBT-ip	0.497*	[0.4942, 0.4999]	0.02075	0.498*	[0.4964, 0.4996]	0.0072
	COMB	0.498*	[0.4955, 0.4998]	0.0171	0.500	[0.4983, 0.5008]	0.2274
	MED	0.500	[0.4964, 0.5025]	0.3632	0.500	[0.4972, 0.5020]	0.3659
	TAU	0.501	[0.4971, 0.5055]	0.27015	0.501	[0.4984, 0.5033]	0.2435

* P<.05; Note: Threshold = 3 or more seizures/day; Subjective = uses self-report rate of seizures by patients; Overall= uses patient's observed rate of seizure after end of trial; Seven=uses patient's observed seizure rate for the previous seven days.

Note: cognitive behavioral informed psychotherapy (CBT-ip), sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and treatment as usual (TAU)

Table 3. Weekly Cluster Events, by Treatment Arm and Definition

Definitions	Arm	Cluster Events			Relative Increase Events		
		Reduction	95% CI	P	Change	95% CI	P
Threshold	CBT	0.08*	[0.16, 1.01]	0.0416			
	COMB	0.07*	[0.09, 0.04]	<.0001			
	MED	0.01	[0.04, 1.02]	0.2058			
	TAU	0.07	[0.24, 1.14]	0.24215			
Subjective	CBT	0.04	[0.14, 1.07]	0.21795	0.06^	[0.14, 1.03]	0.09945
	COMB	0.10*	[0.14, 0.05]	<.0001	0.06*	[0.10, 0.01]	0.0107
	MED	0.01	[0.08, 1.06]	0.36645	1.01	[0.07, 1.09]	0.406
	TAU	0.01	[0.19, 1.22]	0.47775	0.02	[0.14, 1.11]	0.36465
Overall	CBT	0.08*	[0.16, 0.00]	0.0258	0.08*	[0.15, 0.01]	0.01355
	COMB	0.09*	[0.12, 0.05]	<.0001	0.10*	[0.16, 0.03]	0.0015
	MED	1.01	[0.09, 1.12]	0.4387	0.03	[0.12, 1.07]	0.2775
	TAU	0.07	[0.24, 1.13]	0.2342	0.08	[0.22, 1.09]	0.1589
Seven	CBT	0.09*	[0.16, 0.01]	0.0151	0.05*	[0.09, 1.00]	0.02755
	COMB	0.07*	[0.12, 0.01]	0.0089	0.05*	[0.10, 1.01]	0.05
	MED	0.03	[0.09, 1.03]	0.1742	0.00	[0.05, 1.05]	0.4629
	TAU	1.04	[0.11, 1.20]	0.31515	1.02	[0.05, 1.11]	0.26845

^P<.10, * P<.05; Note: Threshold = 3 or more seizures/day; Subjective = uses self-report rate of seizures by patients; Overall= uses patient's observed rate of seizure after end of trial; Seven=uses patient's observed seizure rate for the previous seven days.

Note: cognitive behavioral informed psychotherapy (CBT-ip), sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and treatment as usual (TAU)

Table 4. Secondary Outcomes at Trial Baseline

Cluster	Outcome	Mean	95% CI	DF	T	P
BDI-II						
No	Worse*	15.55	[10.92, 21.34]	1, 32	4.91	0.01695
Yes		23.61	[19.00, 28.63]			
BAI-II						
No	None	21.88	[15.08, 29.86]	1, 26	1.07	0.15555
Yes		26.75	[21.08, 32.78]			
BIS						
No	Worse*	61.01	[54.93, 66.85]	1, 32	6.62	0.00745
Yes		71.31	[65.61, 76.52]			
DES						
No	Worse*	11.13	[7.82, 15.61]	1, 32	4.8	0.0179
Yes		18.09	[13.41, 23.94]			
DTS						
No	Worse^	44.00	[28.76, 62.60]	1, 32	2.71	0.0548
Yes		63.31	[48.10, 78.99]			
HAM-D						
No	Worse*	10.50	[7.64, 14.11]	1, 26	6.25	0.0095
Yes		15.55	[13.60, 17.67]			
QoL						
No	Worse*	45.18	[37.66, 52.94]	1, 32	2.97	0.0472
Yes		37.21	[31.90, 42.86]			
SCL-90-R						
No	Worse^	92.36	[69.81, 119.88]	1, 32	1.86	0.0913
Yes		118.03	[91.24, 149.46]			
GAF						
No	None	51.10	[47.83, 54.34]	1, 32	1.18	0.14305
Yes		49.05	[47.01, 51.09]			
OHS						
No	None	2.67	[1.94, 2.92]	1, 9	0.23	0.3202
Yes		2.80	[1.85, 2.98]			
CGI-SEV						
No	Worse*	4.09	[3.67, 4.49]	1, 32	11.55	0.0009
Yes		4.96	[4.62, 5.26]			
CGI-IMPV						
No	None	4.18	[3.43, 4.87]	1, 32	0.02	0.45005
Yes		4.13	[3.74, 4.50]			
ER Visits						
No	None	0.27	[0.10, 0.74]	1, 32	0.89	0.17675
Yes		0.48	[0.24, 0.95]			
MD Visits						
No	None	0.82	[0.15, 4.56]	1, 32	0	0.4959
Yes		0.83	[0.38, 1.81]			
HX Visits						
No	None	0.09	[0.01, 0.63]	1, 32	0.66	0.2107
Yes		0.22	[0.08, 0.59]			

^ P<.10 , *P<.05;

Table 5. Overdispersion (Supplemental)

	Seven	Overall	Subjective	Sub/observed
CBT-ip	1.0	1.67	1.0	1.8
COMB	1.4	2.45	2.1	1.2
MED	1.1	1.77	0.9	1.1
TAU	1.0	1.52	0.9	1.8

Note: Threshold = 3 or more seizures/day; Subjective = uses self-report rate of seizures by patients; Overall= uses patient's observed rate of seizure after end of trial; Seven=uses patient's observed seizure rate for the previous seven days.

Note: cognitive behavioral informed psychotherapy (CBT-ip), sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and treatment as usual (TAU)

Table 6. Effect size, by treatment arm (Supplemental)

		3 or more	No 3
Subjective	CBT-ip	3.50	7.00
	COMB	6.83	3.50
	MED	2.33	3.73
	TAU	12.25	7.00
Overall	CBT-ip	3.71	4.31
	COMB	7.00	4.26
	MED	3.33	4.82
	TAU	6.21	6.21
Seven	CBT-ip	3.89	4.67
	COMB	7.47	4.52
	MED	3.23	3.50
	TAU	4.20	4.00

Note: Threshold = 3 or more seizures/day; Subjective = uses self-report rate of seizures by patients; Overall= uses patient's observed rate of seizure after end of trial; Seven=uses patient's observed seizure rate for the previous seven days.

Note: cognitive behavioral informed psychotherapy (CBT-ip), sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and treatment as usual (TAU)

Figure 1. Weekly Total Cluster Events, by Definition

Legend

1. Y axis: total number of weekly cluster events, 0-4 clusters
2. X axis: time (weeks)

Note: Threshold = 3 or more seizures/day; Subjective = uses self-report rate of seizures by patients; Overall= uses patient's observed rate of seizure after end of trial; Seven=uses patient's observed seizure rate for the previous seven days.

Note: cognitive behavioral informed psychotherapy (CBT-ip), sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and treatment as usual (TAU)

Figure 2. Total Weekly Relative Increase Events, by Definition

Legend

1. Y axis: total number of weekly cluster events, 0-4 clusters
2. X axis: time (weeks)

Note: Threshold = 3 or more seizures/day; Subjective = uses self-report rate of seizures by patients; Overall= uses patient's observed rate of seizure after end of trial; Seven=uses patient's observed seizure rate for the previous seven days.

Note: cognitive behavioral informed psychotherapy (CBT-ip), sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and treatment as usual (TAU)

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Title: Psychogenic Non-epileptic Seizure Clusters: Description and Theory Considered

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Summary

Objective: Research is presently lacking concerning how to describe and explain seizure clusters in patients with PNES. This review details how clusters have been defined so far in both the epilepsy and PNES literatures. In addition, theories as to why seizures cluster for patients with PNES are also introduced and considered. The aim of this study is to provide a foundation from which theory on seizure cluster definition and explanation may be advanced.

Key words: PNES, seizure clusters, description and theory

Psychogenic Non-epileptic Seizure Clusters: Description and Theory Considered

Introduction

Psychogenic non-epileptic seizures (PNES) are events that are often similar in outward manifestation to epileptic seizures but unlike epileptic seizures, have no corresponding epileptiform activity ⁽¹⁾. One similarity between epileptic seizures and PNES is seizure events occur in bouts or clusters in some patients. Interestingly, most research on seizure clustering is found almost exclusively in the epilepsy literature (see Bodde et al.) ⁽²⁾ while research on clustering for patients with PNES is left wanting. Although seizure clustering is acknowledged in the PNES literature ⁽³⁾, there are currently only two studies known to the authors empirically examining clusters in patients with PNES^(4, 5).

Along with limited empirical research examining seizure clusters in patients with PNES, there is currently a paucity of literature concerning the theory as to why seizures present in clusters; moreover, theory is even lacking on how to best conceptualize and define seizure clusters in PNES. As a consequence, there is little or no theoretical framework for clinicians and researchers about how to describe, explain, predict, and hopefully prevent and reduce seizure clusters for patients with PNES. The present manuscript provides a review of how seizure clusters have been described in the literature. In addition, using current theories of PNES, possible frameworks for explaining seizure clustering in the population with PNES will be explored. The intent of this study is to provide a foundation from which theory on cluster definition and explanation may be advanced.

Defining clusters in PNES

The following outlines several approaches used for the identification of clusters. These approaches can take two general forms: patients are either identified as having evidence of seizure clustering without clusters themselves being identified, or alternatively, clusters are specifically identified as events. Each will be reviewed and the relative benefits and limitations of each approach will be considered.

Stochastic process

One approach of examining seizure clustering in the epilepsy literature is to use stochastic modeling to identify patterns of seizure occurrence that may be indicative of clustering. Balish et al. ⁽⁶⁾ defined clustering as dependency between the expected daily seizure rate and previously observed seizures, as evidenced by a significant autoregressive coefficient value when using generalized linear modeling. In most cases, dependency was positive, where an increase in seizure count on a previous day increased the subsequent expected daily seizure rate, although some instances of negative dependency were also observed.

Hopkins et al. ⁽⁷⁾ described seizure clustering as an increase in days with 2 or more seizures and/or an increase in the number of “short” interseizure intervals. Using this definition, Milton et al. ⁽⁸⁾ evaluated clustering using a time series analysis, where deviations from what would be expected from a Poisson process for: 1.) the number of days with 0, 1, 2, 3 ... seizures; 2.) the number of days between seizures (i.e., interseizure interval) 3.) the change between in the interseizure interval (i.e., does the time between seizures change); and 4.) the days until the next seizure, all served as

evidence for clustering. A limitation of using a Poisson process to evaluate these models is it assumes seizure occurrences are independent of each other (i.e., where seizure events may in fact be related but this fact may not be evidence of clusters), along with assuming the seizure rate is constant. In addition, deviation from a Poisson process does not necessarily indicate deviation from a random process; that is, the process may be random but not as defined using a Poisson process (e.g., uniform process).

Taubøll et al. ⁽⁹⁾ defined clustering as “... the occurrence of a day with seizure(s) increased the susceptibility of having another” (p. 160) and used three criteria when determining of seizure clustering. Specifically, if: 1.) a patient’s seizure profile had evidence of not being a random process, as indicated by a Wald–Wolfowitz runs test when patients had several days with or without seizures, 2.) the number of days with several seizures or no seizures exceeded what would be expected from a Poisson distribution, and 3.) there was evidence that a seizure occurrence was a function of a previous seizure event (which assumes a stationary rate), as evidenced by an autoregressive function with a significant autocorrelation coefficient value, then it was concluded that the patient had seizure clustering.

Although stochastic modeling provides an avenue for identifying if a patient has seizure clusters, the approach is not without limitations. For instance, several stochastic approaches require a patient’s seizure rate to be stationary ⁽⁶⁻⁹⁾. While this requirement may be feasible for naturalistic observations, it cannot be assumed that the seizure rate for patients enrolled in a treatment trial or receiving therapy would remain constant; hopefully, it would be decreasing. In addition, in order to establish if

a patient has clustering or not, several weeks or months of data must be collected. For instance, the mean seizure diary length (in days) of the aforementioned studies was 382⁽⁶⁾, 347⁽⁹⁾ and 217 for men and 247 for women⁽⁸⁾.

Although stochastic models use a patient's own seizure observations in determining if clustering exists, clusters, as events, are never identified. The consequence of not identifying a cluster as an observable event is straightforward: without clusters themselves being observed, it is difficult for clinicians and researchers to evaluate if a patient's clusters are improving or getting worse; instead, they are restricted to only determining if there is or isn't evidence of clustering *during treatment*, unless seizure diaries were provided prior to treatment. Thus, not only do these methods require several days of observation, but also, identification of clustering may take place well into or even after treatment has been delivered. Finally, stochastic modeling requires several resources, such as advanced knowledge of statistical modeling and access and training with statistical software; resources that may not be available to many clinicians.

Threshold

A common definition of cluster is based on a general formula whereby a cluster is identified as an event when the number of seizures a patient has surpasses some predetermined threshold during a specified interval of time⁽²⁾.

The most common threshold used in the epilepsy literature is 3 or more seizures occurring in 24 hours^(2, 10-12). The 3 or more seizure definition was developed originally by Huat et al.^(11, 12), who found that epileptic seizures occurring within 8

hours of each other were more concordant (i.e., same hemisphere foci) than discordant; this definition was then extrapolated to 3 seizures in 24 hours⁽¹²⁾.

Although Haut et al.'s⁽¹²⁾ definition is based off of observed concordance between seizures in epilepsy, the reasoning behind this definition does not hold for PNES, although defining a cluster as 3 or more seizures has been examined for patients with PNES^(4, 5).

The benefit of using a threshold approach is the definition of seizure cluster is identical between patients, within patients over time, and across patient populations, thus making it nomothetic in nature. This operationalization is not only easy to implement clinically and in research, but it also can be used shortly after the initiation of treatment or therapy. Perhaps the most important benefit of a threshold approach is clusters are identified as observable events, thus making it possible to evaluate if cluster frequency is improving, getting worse, or is static.

However, there are certain drawbacks associated with using a one-size-fits-all approach to defining a cluster event. For instance, some patients will never be considered as having clusters if they never present with a given number of seizures, while others will be considered to always be having clusters because they never drop below some number of seizures. Likewise, cluster reduction in one patient may not occur even if the reduction in seizures is large but said reduction fails to drop below the threshold (e.g., 15 to 3 seizures/day); conversely, a patient who has only 1 fewer seizure each day may be seen as having a reduction in clusters (e.g., 3 to 2 seizures/day). Implicit with these shortcomings is cluster identification does not take into account for a patient's typical seizure frequency, nor does cluster identification

change with a patient's changing seizure rate—the tradeoff of a nomothetic approach to cluster identification.

As noted previously, Haut ⁽¹²⁾ formed the “3 seizures or more” definition because seizures occurring within 8 hours of each other appeared to be concordant or similar, thus indicating they were related events; however, this has only been examined in patients with epilepsy and not PNES. Another possible interpretation of a threshold definition is the notion that X number of seizures are “many”, relative to a Y time interval. The interpretation of a cluster being “many” events may be intuitive in concept, but operationalizing “many” is not intuitive, especially when considering the large variability of seizure frequency between and even within patients. Thus, justification of a certain threshold of seizures for a given interval of time as the definition of a cluster event, which would be representative of an entire population with PNES, may prove difficult.

Deviation from typical pattern

Clusters have also been defined as a seizure pattern that is different than a patient's typical seizure pattern, such as a “pattern distinguishable from the patient's usual seizure pattern” ⁽¹³⁾ and “seizure cluster pattern is observable, stereotyped, and recognizably different from the patient's other non-cluster seizure activities (if any)” ⁽¹⁴⁾. Although perhaps intuitive in concept, this definition is difficult to operationalize and implement in practice. For instance, it may be difficult to establish a patient's typical seizure pattern—that is, what duration is required to establish a patient's typical seizure pattern and how does one know the seizure pattern has not been

affected by therapy or other known and unknown events? Because of recall bias, misremembering, and false memories, it is also difficult for patients, partners, or caregivers to accurately recall what the typical seizure pattern was prior to therapy or treatment. In addition, deviation from the typical seizure pattern would not necessarily mean evidence of a seizure cluster.

Relative increase

A related but distinguishable approach of the deviation from the typical pattern definition of cluster would be to compare the number of seizures a patient has had for a given time interval with that of the patient's typical number of seizures. This definition was examined in the PNES literature where a "relative increase" event was identified when the number of seizures occurring in a day statistically exceeded a patient's expected seizure rate ⁽⁴⁾. Moreover, a "cluster" event was defined as three or more seizures in a day statistically exceeding a patient's expected seizure rate. By making three or more seizures a necessary but not sufficient condition of a cluster event, this definition is therefore an extension of the threshold definition, though an argument can easily be made that relative increase events without a threshold could also be considered a cluster event. For clarity, definitions that identify a cluster event using a relative increase approach, with or without a threshold, will be referred to here as simply a "relative increase" approach.

There are several benefits with using the relative increase approach. First, because clusters are defined as a relative increase in the number of seizures for a given day, clusters are therefore an observable event. In general, approaches that identify

clusters as events have the benefit of being observable outcomes, thus allowing cluster improvement to be evaluated clinically or in research. Because clusters are identified as events, possible antecedents and consequences associated with each of these events can be subsequently identified. Although the threshold approach also identifies clusters as events, it does so solely as a function of seizure count; thus, those who typically have several seizures will usually present with clusters, therefore making it difficult to identify possible unique triggers and outcomes associated with cluster events, while the relative increase approach allows for triggers and outcomes to be identified for only days which are by definition abnormally high.

Another benefit of the relative increase definition is it can be implemented in clinical and research settings using a Poisson distribution, as illustrated in ⁽⁴⁾. Because cluster events are defined identically between and within patients, while also being predicated on a patient's individual typical seizure rate, the relative increase approach is *both* nomothetic and ideographic (i.e., cluster events retain the same meaning from patient to patient, but identification of cluster events remains unique to an individual patient). Therefore, cluster events in patients who typically have several seizures and patients who typically have few seizures can be examined, identically.

It is also important to note there are several shortcomings associated with the relative increase approach. Although “was this day worse than what would be expected” may be a natural clinical question, the reference for “expected” number of seizures is not immediately clear. As illustrated in ^(4, 5), there are several different possible and justifiable expected seizure rates from which to choose. For instance, using a patient's subjective “typical” seizure count before initiation of therapy may be

helpful; however, this definition may not remain realistic by the end of treatment, where the seizure rate has presumably decreased, thus making clusters more likely to be identified (or vice versa). On the other hand, a patient's observed seizure rate for the entire duration of therapy may not provide a better representation of a patient's seizure rate at any specific point during therapy if the patient's seizure rate is changing. In addition, because a patient's actual seizure rate for the entire treatment period is known only after treatment completion it therefore cannot be used to identify clusters at any point during therapy.

Another possible reference for expected seizure rate would be the observed seizure rate of the current week or previous seven days. Both of these expected seizure rates accommodate a patient's changing seizure rate, while also being available within the second week of treatment. The weakness with these local expected seizure rates is there is no way of knowing how long of a duration the rate window should be — one week, 2 weeks, etc. However, because clinicians often review patient seizure logs on a weekly basis, using a week or previous seven days as a local expected seizure rate might be the most intuitive option.

Summary

One underlying weakness true for all cluster definitions reviewed here is none of these methods provide clear evidence of a cluster event or clustering in PNES per se. That is, whether the number of seizures exceeds a given threshold (threshold), statistically exceeds what is expected (relative increase), deviates from random, or seizures appear to be a function of previous seizures (stochastic process), these approaches rely solely on operational definitions, not theory, as to why these results

are evidence of clusters. For instance, these approaches cannot distinguish a cluster from having a “bad day” with several seizures. To date, there is little or no theory as to what a cluster of seizures should look like. This dearth in theory as to what a cluster of seizures may look like may be due to theory lacking in general concerning what causes clusters in the population with PNES; a consideration of the next section.

Theories of Clustering in PNES

In the absence of a working theoretical framework, it is difficult to not only evaluate how best to describe and define seizure clusters, as evidenced in the previous section, but also how best to explain seizure clusters as a phenomenon, predict them in the future, and ultimately how best to prevent and reduce clusters in patients with PNES. The following presents four different possible theories as to why seizure clusters may occur in the population with PNES. The first three theories reveal how seizure clusters can be accounted for by an overall theory explaining PNES. The fourth provides a specific theory for why seizures (and behaviors in general) may cluster. In addition, how clusters may be defined within each theory of clustering will also be considered; some theories may invite a new definition of cluster, while others may correspond with the previously outlined definitions.

1. Trigger theory

Bodde et al. ⁽³⁾ provide a theoretical model that suggests PNES are caused by several levels of contributing factors, briefly: 1) psychological etiology, including factors believed to be involved with the cause of PNES, such as traumatic events (i.e., sexual, physical, emotional abuse, etc.), 2) factors of vulnerability, such as general

predispositions of psychosomatic symptoms (e.g., age, personality, gender, and neuropsychological impairments and organic factors), 3) influences on how PNES is shaped and expressed due to symptom modeling (i.e., acquiring symptom based on observing a genuine symptom, which can include the self or others), 4) situational triggers that incite seizures, such as reduction of anxiety, psychological mechanisms (e.g., disassociation and somatization) that transfer emotional states into seizure behavior, and other stressors including family and relationship conflicts and 5) finally, prolongation factors that contribute to maintenance of PNES, such as coping and secondary reinforcement, which explains why PNES can persist, be resistant to treatment, and become chronic. This model is summarized in Table 1.

Though Bodde et al. ⁽³⁾ provide an overall explanation of PNES, their model also accounts for clusters in particular. Specifically, they hold that triggering factors that evoke seizures, such as situational triggers, but also mechanisms that transfer an emotional state into a seizure such as dissociation and somatization, are responsible for why seizures occur on certain times and days, have periods of remission, and present in clusters. Although this theoretical model explains why seizure clusters occur, the model does not detail what a cluster is or how it should be defined. Because a cluster is not specifically defined, any of the cluster definitions provided in the previous section could be used to describe clusters, although some definitions may lend themselves to the Bodde et al. ⁽³⁾ particular theory better than others.

For instance, the relative increase approach of cluster identification is especially well-suited for the trigger model, as it allows for researchers and clinicians the ability to examine possible triggers leading up to days in which more seizures

occurred then would be expected. Because clusters are not necessarily abnormal events for the trigger model, the threshold approach would allow the identification of triggers leading to days when the number of seizures occurring exceeded the established threshold. However, if a patient generally has over or under the established threshold, it would be difficult to identify triggers associated with clusters, as these events would always or never be occurring, respectively. On the other hand, it may be difficult to identify specific triggers when using stochastic modeling, as these approaches do not identify specific events that can be used to trace back possible preceding triggers.

2. Anticipatory theory

Brown's ⁽¹⁵⁾ conceptual model of PNES holds that seizure events are caused by the activation of “rogue” mental representations -- representations of illness that can form from direct exposure to having seizures or others having seizures, found in one's social circle or media, or due to suggestion from authority figures, such as healthcare workers. Brown notes that there are several possible factors that can activate these rogue mental representations, such as worry and rumination, anxious anticipation of further seizures, interoceptive cues signaling seizure onset, behavioral reinforcement (negative and positive), and illness behaviors, such as avoidance and reassurance seeking.

Brown's general theory of PNES could be extended to explain why seizures occur in clusters. Though not specifically explored by Brown, what is clear from this model is if a patient has a seizure, the anxious anticipation of a subsequent seizure

may, in concert with interoceptive cues signaling an oncoming seizure, elicit another seizure, thus causing a chain reaction - a type of feedback loop - where seizures beget more seizures. Here, a cluster may be described as one or more seizure events occurring sequentially and following closely in time with one another. Although this description may be intuitive, time between seizures will vary by patient, as the duration of a seizure varies across patients, as does the time between a patient's onset anticipation of a subsequent seizure following a previous seizure; thus, seizures could occur seconds, minutes, or even hours between each other.

This description of clustering could naturally be defined as dependency between observations and evidenced by the presence of autocorrelation using stochastic modeling. However, this would require seizure frequency to be a stationary process, which is not a reasonable assumption for patients who are receiving treatment. Thus, a non-stationary autoregressive process would need to be used, which may prove difficult. In addition, the relative increase approach could be used to define a cluster for this model, where having 2 or more seizures occurring above what is expected in a defined interval of time is defined as a cluster event. Because Brown's model would not require clusters to be abnormal occurrences, the less restrictive threshold approach could similarly be used, where 2 or more seizures in a day (or some other time interval) is considered a cluster.

3. Tipping-point / State-transition model

One theory of seizure occurrence is from the learning theory fear-avoidance model used for PNES by LaFrance⁽¹⁶⁾, and holds that an event may occur when

emotional, cognitive, or physical symptom buildup becomes too great that the tipping-point is reached. This model involves predisposing, precipitating, and perpetuating factors as component contributors to seizure generation ⁽¹⁾. A seizure follows an immediate or recent precipitant. Just as a kettle releases steam intermittently over time and whistles once the boiling point is achieved, so do seizures present – intermittent seizures occur as emotional buildup accumulates over time due to stressors. To apply to clusters, once the buildup is too great, a single seizure or a cluster of seizures results. In this model, the buildup is converted into the somatic manifestation of a seizure. Clusters are differentiated from individual seizures only by the proportional magnitude of the buildup -- small buildup leads to individual seizures, great buildup leads to a cluster of seizures.

Along with describing periods of high stress, patients also describe seizures occurring during a period of less stress, or during the "let-down" period. Seizures may occur after a stressful period has passed and the individual is in a relaxed state. Patients describe confusion about the seizures, noting, "I wasn't stressed - I was away from it all on vacation, and I had a seizure." The tipping-point may not be just at the climax, but in the falling action or denouement of the patient's narrative. Thus, the tipping-point theory of clustering may be evidence for a broader state-dependent process (instead of trait), where *transitions* between states are a catalyst for clusters.

The tipping-point theory of clusters describes clusters as a burst of seizures, thus indicating that a cluster would be several seizures occurring in a short interval of time. Whereas quantifications of “several” seizures and “short” interval are open to interpretation, a burst of seizures could be broadly defined as more seizures occurring

than expected (relative increase definition) or a set number of seizures occurring in a specific interval of time (threshold definition).

4. Packet theory

Packet theory, a model from the animal behavioral literature, also provides a possible explanation for seizure clusters or “packets”⁽¹⁷⁾. It has long been observed that certain operant behaviors sometimes occur individually while other times in stereotypical, rapid succession –bouts – such as lever presses, keypecks, and drinking^(18, 19). Kirkpatrick and Church⁽²⁰⁾ examined bout behavior in rats by measuring the time between successive magazine behaviors (i.e., inter-response time or IRT) across different food delivery reinforcement schedules (i.e., fixed, random, tandem time), finding that bouts were invariant across the different reinforcement conditions. This finding was consistent with previous literature showing that relatively short IRT’s are unaffected by experimental manipulation when compared with larger IRTs^(21, 22). Because bouts were insensitive to reinforcement manipulation, Kirkpatrick and Church concluded that a bout could be distinguished from individual behavior and as such, can be thought of as its own unit of behavior-- a single packet.

Packet theory as an explanatory framework for seizure clusters is straightforward: a cluster of seizures could be conceptualized as a bout of responses– a stereotypical rapid succession of seizures – and thus its own unit of behavior, separate from an individual seizure. As a framework, Packet theory provides elements of both description and explanation and these elements could be extended to seizure

clustering. Although a full account of Packet theory is beyond of the scope of this paper, a brief summary is provided.

Kirkpatrick and Church ⁽²⁰⁾ note that because of their multi-response nature, bouts can be described in terms of temporal structure: the time between bouts, IRT, follows an exponential distribution and the number of responses for a given bout follows a geometric distribution. Thus, the probability of a response within a bout reduces as the time between two behaviors increases; likewise, the probability of a response decreases as the number of responses increase. What is particularly interesting is Kirkpatrick and Church ⁽²⁰⁾ found these distributions held, regardless of the reinforcement schedule that the rats were trained on (i.e., fixed, random, tandem).

Kirkpatrick ⁽¹⁷⁾ holds that bouts are generated by the mean time remaining until food (reinforcement) as a function of time for a given reinforcement interval, called the conditional expected time (CET) function. Briefly, during conditioning, 1) after each reinforcement occurs, an expectation for duration until reinforcement is generated (perception); 2) over time, the average of these expectations constitutes the conditional expected time function, and the CET is specific for each type of interval (fixed, random, tandem) (memory); 3) thus, behaviors occurring in anticipation of reinforcement are evoked by a) the inverse function of the CET, which is a probability of a packet resulting or not, and, b) n , a response parameter, which is the expected number of responses for a given interval (and is thus the sum of the probabilities) (decision).

Packet theory provides a versatile framework for accounting for seizure clustering. A cluster as a bout is defined as its own unit of behavior and is

differentiated as a separate process from individual seizures. Bouts are generated as a function of the expected time until reinforcement, and the expected time is a result of prior interval reinforcement conditioning, although the presentation of bouts is invariant to type of reinforcement schedule. Thus, variability between patients in terms of when clusters present can be accounted for by different learning histories while the presentation of clusters themselves can be accounted for by the theory.

Conclusion

Although each theory here has been considered with each definition, it is clear that in general, multiple definitions of cluster could be used to test a given theory. However, it appears that some definitions of cluster, namely those that identify a cluster as an event, are better suited for testing the theories reviewed here. In general, definitions that use stochastic modeling to identify clustering usually require patient seizure rates to remain stationary, a property that would preclude cluster investigation in treatment settings. In addition, because stochastic models are unable to identify clusters as events, this limitation makes testing theories of clustering particularly difficult. For instance, clusters would have to be observed as an event occurring after an identified antecedent in order for trigger theory to be tested; likewise, clusters would have to be observed as an event following a patient report of experiencing high levels of emotional distress (or lack thereof) for the tipping-point theory to be tested.

Because the threshold and relative increase definitions identify a cluster as an event, distinguishable from an individual seizure event, these definitions naturally correspond with packet theory, which identifies a bout as its own unit of behavior, also distinguishable from an individual response. Finally, as previously noted, an

autoregressive model assessing dependency between seizure events may be a natural way to test the anticipatory model, where seizures beget seizures, though again, a non-stationary stochastic process would need to be used, which may prove difficult. On the other hand, both a threshold and relative increase definition could be used to test the anticipatory model as these definitions could identify instances whereby multiple seizures occur sequentially within a defined time interval.

Although the threshold and relative increase definitions both may be better suited for evaluating theory of seizure clustering, it should be reiterated that there are several benefits of using a relative increase definition over a threshold definition, as discussed in the first section of this paper and explored in detail in ⁽⁴⁾. Thus, the benefits of certain definitions, along with conditions for each definition (i.e., threshold values, interval lengths, references of expected seizure rate), should be considered carefully when testing a theory of clustering for PNES.

The purpose of this review was to provide an overview of possible definitions of seizure clusters and theories as to why seizures present in clusters in the PNES population. Also considered was how each definition of seizure cluster could accommodate each theory of cluster. Illustrated by the dialog between seizure cluster description and explanation is a “chicken-and-the-egg” conundrum: can we have a theory of seizure clustering without a clear definition of what a cluster is? Then again, can we define a cluster without a theory to account for how and why clusters present in the first place? This paradox creates confusion as to which should even be studied first: description or explanation? Although this review does not resolve this conundrum, it is our hope that by outlining different possible definitions and theories

of PNES clustering, research in this area may be continued, aiding clinicians and researchers in ultimately informing how to best treat, and hopefully prevent, seizure clusters in patients with PNES.

Table 1. Trigger theory of clusters

	1	2	3	4	5
Level	Psychological Etiology	Vulnerability	Shaping	Triggering	Prolongation
Factor	“Cause” such as traumatic event, abuse, etc.	Predisposition, such as personality, organic reasons, etc.	Symptom modeling	Factors that evoke seizures, such as stressors, primary gain	Factors which maintain PNES, such as secondary gain

Table 2. Anticipatory theory of cluster

Activating factors	What is activated	Behavior
Anxious anticipation of subsequent seizure Interoceptive cues signaling a seizure	➔ 'Rogue' Mental Representations of physical illness	➔ Nonepileptic Seizure

Table 3. Tipping-point / State Transition Model

Stressors		Proportional Buildup		State transition		Behavior
<ul style="list-style-type: none">• Being cutoff in traffic Major argument with significant other	➔	<ul style="list-style-type: none">• Small buildup• Large buildup	➔	Tipping point (or Release point)	➔	<ul style="list-style-type: none">• Seizure• Cluster

Table 4. Packet Theory

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