VIEWPOINTS

News from the ILAE British Chapter 2018 Annual Scientific Meeting

Produced in association with ACNR

The 2018 Annual Scientific Meeting of the British Branch of the ILAE, held in Birmingham on 26-28 September 2018, brought together more than 350 epilepsy researchers and healthcare professionals from across the British Isles. In a varied and busy programme that included plenary sessions, sponsored satellite symposia, a "how to" session, and an expert-led poster session, delegates heard news of the latest research from across the country in a broad range of epilepsy topics.

At the meeting Professor Matthew Walker took over as President of the British Branch of the ILAE, and thanked the outgoing President Dr John-Paul Leach for his hard work and considerable contribution to epilepsy education and research in the UK.

Several keynote presentations were made at the meeting by world-renowned epilepsy experts, and some of these are outlined here in this newsletter. During the LivaNova satellite satellite symposium entitled “Where is the potential? Measuring the effects of neuromodulation,” Professor Kristl Vonck introduced the concept of a pre-stimulation evaluation protocol for identifying the right candidates for neurostimulation therapies (page 3).

Other presentations included: the latest thinking from Dr Christoph Bernard on the “diathesis–epilepsy model” which may explain the vulnerabilities of patients to comorbid depression and cognitive impairment (page 5); and a presentation from Dr Amy McTague on the potential application of gene panels in identifying the aetiology of severe early onset epilepsies (page 5).

The ILAE meetings is one of my highlights of the year. It is a great opportunity to see old friends, but more importantly it enables people from a broad range of disciplines including neurologists, neurosurgeons, neuropsychiatrists, neuroscientists, nurses, psychologists and technicians to come together to participate in a truly multidisciplinary meeting.”

Professor Matthew Walker,
President of the ILAE British Chapter

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Prescribing information can be found on the last page.

LivaNova
Health innovation that matters

Real-world experience with VNS therapy

Real-world evidence for the effectiveness of the first closed-loop (responsive) vagal nerve stimulation (VNS) device AspireSR (Seizure Response) was presented by Ramesh Chelvarajah, Consultant Neurosurgeon (Functional & Neurotrauma), University Hospital, Birmingham, during the LivaNova symposium at the ILAE British Conference. This device, which uses ictal tachycardia as a surrogate marker for seizures, can not only reduce seizure severity by preventing electrographic spread of seizures but also reduces seizure frequency in patients with both focal and generalised seizures.

In an analysis of patients treated with responsive VNS (rVNS) over a 3-year period at the Queen Elizabeth Hospital Birmingham (QEHB), Ramesh Chelvarajah described how 59% (30 of 51) of patients had ≥50% reduction in seizure burden post-AspireSR® therapy (Hamilton et al 2018). Of these, 21 (41%) reported ≥80% reduction in seizure burden and 3 patients (6%) had no seizures after completing ramping up of rVNS therapy (Hamilton et al 2018).

Commenting on these data, Mr Chelvarajah observed that "AspireSR achieved an earlier response than observed in previous studies, with 59% of patients reporting significant benefits after a mean follow-up of only 13 months."

Experience with conventional VNS therapy at the QEHB found that the seizure burden was reduced by ≥50% in 53% (33 of 62) of patients at a mean follow-up time of 9.5 years. Upon switching from conventional VNS to rVNS therapy with AspireSR, 19 of 62 patients (31%) reported a further improvement in one or more McHugh categories. Overall, a ≥50% reduction in seizure burden was observed in 44 of 62 patients (71%) (Figure 1) (Hamilton et al 2018).

Mr Chelvarajah concluded "With a change from conventional VNS to AspireSR, we can expect that approximately one-third (35%) will have a ≥80% seizure burden reduction, another one third (35%) will have a 50-79% benefit and one-third (27%) of our patients will have a <50% benefit. Only 2% of patients had a negligible response in this study." (see Figure 1).

McHugh classification for measuring the response to VNS

McHugh proposed a novel scale for assessing VNS, which considers both the frequency and severity of seizures as well as more specific benefits such as external magnet efficacy. This allows physicians to more accurately gauge the benefits of VNS reported by patients who may experience an improvement in seizure severity even in the absence of a change in seizure frequency.

Class I	80-100% reduction in seizure frequency Class IA: improved ictal or post-ictal frequency Class IB: no improvement in ictal or post-ictal severity
Class II	50-79% reduction in seizure frequency Class IIA: improve ictal or post-ictal frequency Class IIB: no improvement in ictal or post-ictal severity
Class III	<50% reduction in seizure frequency Class IIIA: improve ictal or post-ictal frequency Class IIIB: no improvement in ictal or post-ictal severity
Class IV	Magnet benefit only
Class V	No Improvement

McHugh JC et al. Epilepsia 2007; 48: 375-8.

> *Based on our experience, we recommend considering a switch to rVNS, particularly in patients who benefit from conventional VNS.*

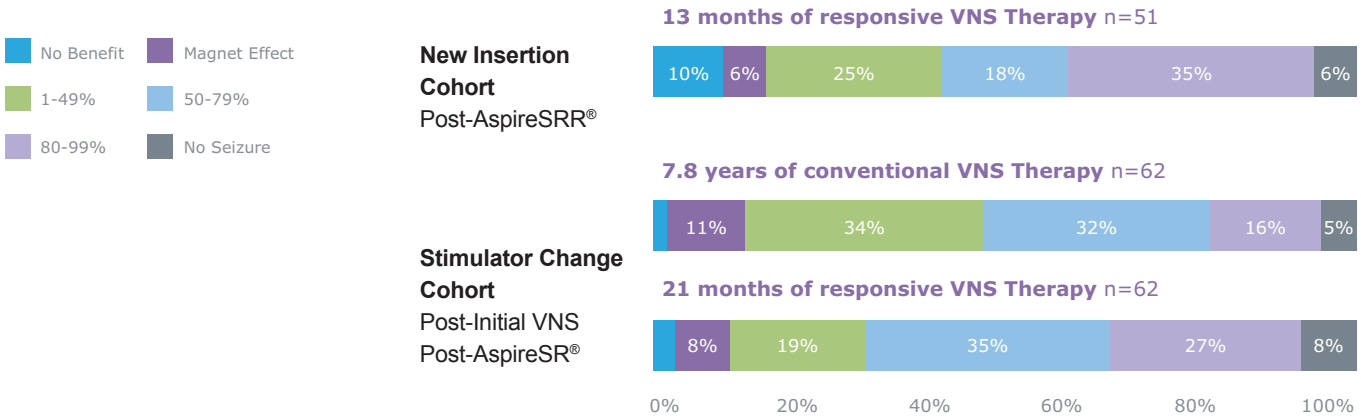

Figure 1. Seizure response to VNS pre- and post-stimulator change to rVNS with AspireSR Adapted from data Hamilton P et al. Seizure 2018; 58: 120-126.

Quantifying the effects of neuromodulation

Mechanisms of vagus nerve stimulation (VNS) are well documented on a brainstem level, with increased noradrenaline (NA) and serotonin release thought to play a major role. However, beyond this level, mechanisms become complex, affecting multiple structures and networks and consensus is therefore lacking.

During the LivaNova satellite symposium, Dr Barbara Wysota, Neurology Consultant, University Hospital of Birmingham explained how new quantitative electroencephalographic (EEG) methods can help to understand how brainstem modulation affects cortical rhythms.

Several studies have highlighted the role of cortical desychronisation in certain frequency bands in which ictal activity typically occurs in response to VNS. New research indicates that measures of spatial synchronisation of EEG during seizures can quantify the effect of closed-loop VNS (Ravan et al 2017). In addition, the impact of seizures on disruption of autonomic function, and specifically changes in cardiac function, can also be quantified using electrocardiography (ECG) to measure cardiac phenomena during a seizure (Ravan et al 2017).

By combining selected features from EEG and ECG, a new composite measure has evolved to quantify the impact of VNS on seizure severity (Ravan et al 2017). These studies show that automated delivery of VNS at the time of seizure onset not only reduces seizure severity by reducing EEG spatial synchronisation but also reduces the duration and magnitude of ictal tachycardia.

A machine learning approach (fuzzy C-means clustering algorithm) using the composite measure of seizure severity was able to accurately discriminate between seizures pre- and post-VNS therapy with a predictive accuracy of 85.85% (overall) and 90.20% for complex partial and secondary generalised seizures (Ravan et al 2017).

Commenting on the significance of these findings, Barbara Wysota observed, “The quantitative features identified in this study on EEG and ECG could be helpful in predicting long-term responsiveness to VNS therapy.

“This study reinforces the importance of the timely delivery of VNS in achieving better control by reducing ictal spread and the duration of seizures as well as reducing the impact of seizures on cardiac function.”

> *By combining selected features from EEG and ECG, a new composite measure has evolved to quantify the impact of VNS on seizure severity*

A rationale approach for identifying the optimum candidates for VNS

To optimise the therapeutic success of neurostimulation for the management of drug-resistant epilepsy (DRE) in candidates unsuitable for surgery, epileptologists need patient-tailored approaches so that the right candidates can be identified based on a priori response prediction.

During the LivaNova symposium, Prof Kristl Vonck, Associate Professor of Neurology, Ghent University Hospital, Belgium introduced the concept of a pre-stimulation evaluation protocol, consisting of a series of rationally chosen investigations that will allow physicians in the future to evaluate the presence of biomarkers for response to various neurostimulation therapies (Carrette et al 2017).

Analogous to the pre-surgical evaluations in DRE patients, the goal of such assessments will be to provide an evidence-based and standardised way to identify whether the epileptic network is likely to be modulated by the chosen neurostimulation modality (Carrette et al 2017). Work is now ongoing to translate these findings into the clinic.

Several lines of evidence support the VNS-induced activation of the vagus nerve–locus coeruleus–noradrenergic (VN–LC–NA) system as the key mechanism in its seizure-reducing effect (Carrette et al 2017). The afferent fibres of the VN project to the nucleus of the solitary tract (NTS) and either directly or indirectly to the LC, the noradrenergic nucleus of the brain. As a result, noradrenaline concentrations are increased in the hippocampus, amygdala and cerebral cortex, which, in turn, are thought to be predictive of the seizure-suppressing effect of VNS therapy (Carrette et al 2017).

A number of non-invasive indirect measures of NA in the brain are currently under investigation as biomarkers for this response prediction. One such measure is the P3 (or P300) component of the event-related potential (ERP) which is modulated differently in VNS responders and non-responders (Carrette et al 2017). Two separate studies have evidenced a significant P3 enhancement following VNS in responders only, one in depression and one in drug resistant epilepsy (Carrette et al 2017).

Another line of ongoing investigation is the autonomic modulation of pupillary diameter by VNS and dynamic biomarkers relating to the heart–brain connection and in particular, peri-ictal changes in heart rate, which may be predictive of VNS response (Carrette et al 2017).

A third promising approach for VNS response prediction comprises the measurement of cortical excitability by means of transcranial magnetic stimulation (TMS). This concept is based on studies by Di Lazzaro et al (2004) which suggested that acute VNS produces a selective and pronounced increase in intra-cortical inhibition which is correlated with clinical outcome. These findings, however, have yet to be replicated in larger populations (Carrette et al 2017).

Finally, there is growing evidence for a genetic predisposition for susceptibility to neuromodulation and, in particular, recent studies which have identified a poor response to neurostimulation in recipients of common single nucleotide polymorphism (SNP) in the gene for BDNF (brain-derived neurotrophic factor), Val66Met, present in a proportion of predominantly Caucasian patients with epilepsy (Carrette et al 2017).

Neurostimulation – The choices today

For a long time, VNS was the only available neurostimulation treatment option. More recently deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) and the Responsive Neurostimulation System (RNS) have also become available in the UK for unsuitable surgery candidates.

As each of these neurostimulation options appear to be similarly effective, a combination of considerations is likely to determine treatment choice during a discussion with the patient, including the personal clinical experience of the physician or the epilepsy centre where the patient is being treated.

Prof Vonck (Gent University Hospital, Belgium) outlined a framework when evaluating key differences in invasiveness and adverse events which may direct the choice between these options (Table 1) (Carrette et al 2017).

She observed that a key benefit of VNS is that it requires a less invasive surgical procedure. However, VNS is associated with stimulation-related side effects such as hoarseness, coughing, dyspnoea or a pain sensation in the throat; although these side effects typically wear off after long-term treatment (Carrette et al 2017).

ANT-DBS and RNS require brain surgery and are associated with the risk of intracranial haemorrhage and/or parenchymal infection. Furthermore, ANT-DBS may be associated with neuropsychological side effect such as depression (Carrette et al 2017).

Table 1. A list of considerations in favour of, or against, available invasive neurostimulation options

Considerations	VNS	ANT-DBS	RNS
Regulatory issues	+	(+)a	(+)b
Generalised epilepsy	+	/	/
Partial epilepsy			
≤2 foci	+	+	+
Multifocal	+	+	/
Children	+	/	/
Invasiveness	+	–	–
Occupation			
Voice	–		
Comorbitities			
Depression	+	–	
Memory impairment	+	–	
Sleep apnoea	–		
SUDEP risk			–

+ in favour of; – against; / not available.
Abbreviations: VNS, vagus nerve stimulation; ANT-DBS, deep brain stimulation of the anterior thalamic nucleus; RNS, Responsive Neurostimulation System; SUDEP, sudden unexpected death in epilepsy; FDA, Food and Drug Administration.
a FDA approval is pending, reimbursed in Europe, not in United States.
b FDA approved, reimbursement varies in United States, not reimbursed in Europe.

Precision medicine in the genomic era

In 2015, Sir Bruce Keogh outlined the NHS's commitment to moving away from a one-size-fits-all approach to healthcare towards a future of precision medicine using genomics (Keogh 2015). Genomics has the potential to improve both patient outcomes by using more targeted treatment approaches and deliver cost-benefits to the health service.

During the opening session at the conference Dr Amy McTague, UCL Great Ormond Street Institute of Child Health observed that there is a strong rationale for using targeted epilepsy gene panels, especially in patients with early-onset and severe (drug-resistant) epilepsies. In a recent paper by Rikke S Møller and colleagues (2016), a pathogenic mutation was identified in 57% of infants with neonatal-onset epilepsies compared with only 14% of children with epilepsy onset between 2 and 9 years, and none with epilepsy onset between 10 and 28 years. The overall diagnostic yield for patients with epileptic encephalopathies was much higher (32%) compared to 17% of patients with generalised epilepsy and 16% of patients with focal or multifocal epilepsy when using a gene panel of 46 epilepsy genes in 216 consecutively referred patients (Møller et al 2016).

However, extensive phenotypic heterogeneity is observed in many monogenic epilepsies, meaning that the correlation between genotype and phenotype is not always straightforward. For example, the phenotypic expression of *SCN2A* genetic variants, one of the first discovered and most common genetic causes of epileptic encephalopathy, ranges from benign familial neonatal/infantile seizures to infantile spasms and severe early-onset epileptic encephalopathies as well as autism/intellectual disability/schizophrenia.

As well as *SCN2A*, another gene (*SCN8A*) which also encodes the voltage-gated sodium channel alpha subunit has been identified and implicated in early infantile epileptic encephalopathies and other epilepsy phenotypes. Individuals with *SCN8A* encephalopathy typically have a mean age of seizure onset of 4-5 months, with multiple seizure types that are often refractory to treatment. The distinguishing features of *SCN8A*-associated early-infantile epileptic encephalopathies are movement disorders, ranging from mild ataxia to choreoathetosis and even quadriplegia. Targeted treatment approaches now in development include the synthetic sodium channel modulator GS-458967 (GS967) which has shown to be an effective treatment in a mouse model of SCN8A encephalopathy.

A growing list of voltage-gated potassium channel genes associated with epileptic encephalopathy have also been identified, including: *KCNQ2, KCNQ3, KCNT1* and *KCNB1* and *KCNA2*. It was in infants with the *KCNT1* gene mutation that one of the first examples of precision treatment approach was identified with the use of quinidine, a potassium channel blocker. Unfortunately, however, only a subset of infants with this more severe 'gain-of-function mutation' appeared to respond to this therapy.

Another rare disorder caused by the mutation in *SLC2A1* gene is Glut-1 transporter deficiency syndrome (GLUT1-DS) which is associated with impaired glucose transport into the brain. The phenotypic presentation of this gene mutation ranges from cognitive decline, microcephaly and refractory seizures to complex movement disorders. Early recognition of this genetic mutation is key in identifying patients who (although refractory to antiepileptic drugs), may have a significant response to a ketogenic diet.

In the future, it is hoped that a greater understanding of the genetics of epilepsy and mechanics of primary and secondary epileptogenesis may lead to more rational treatment approaches, especially in patients with drug resistant epilepsy. Promising investigative approaches which may one day translate to the clinic include: viral-vector-mediated gene transfer for focal epilepsies (Noe et al 2012) and "antisense drugs" which bind to mRNAs and inhibit the production of disease-causing proteins (Schoch KM & Miller TM, 2017).

Recommended reading

Beyond the Ion Channel | The ILAE Genetics Commission Blog. http://epilepsygenetics.net/

EpiPM Consortium. A roadmap for precision medicine in the epilepsies. Lancet Neurol. 2015;14(12):1219-28. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4663979/pdf/nihms726670.pdf

National Organization for Rare Disorders (NORD). Glucose Transporter Type 1 Deficiency Syndrome, https://rarediseases.org/rare-diseases/glucose-transporter-type-1-deficiency-syndrome/

Stress-induced vulnerability to epilepsy and comorbidities

Many patients with epilepsy report that stress can either trigger or increase the severity of seizures. At the conference, Dr Christoph Bernard from Institut de Neurosciences des Systèmes Aix-Marseille Université, France explained the "diathesis–epilepsy model" which provides a conceptual framework to understand how epilepsy and comorbidities (e.g. cognitive deficits and depression) can occur when the threshold for these events are lowered. These thresholds depend on the diathesis (or vulnerability) in each individual, which is determined by multiple factors (both genetic and environmental).

"Beyond genetic influences, past events (eg. a very stressful event) can confer a vulnerability to the development of epilepsy and comorbidities later in life in some individuals," observed Professor Bernard.

These concepts have evolved from the observations in animal models which showed that social stress induced a vulnerability for depression in a subset of rats (Bernard C 2016). After the initial stressor, neither nonvulnerable

nor vulnerable animals display depression-like behaviour, but when exposed to a second (chronic mild) stressor, vulnerable animals displayed depression-like behaviour. Upon further investigation, it was discovered that the initial stressful event left a biological trace – identified as low levels of serum brain derived neurotrophic factor (BDNF) measured after recovery in vulnerable animals. Subsequently, Becker et al (2015) extended this research to investigate the impact of exposure to a social stress on epilepsy and associated comorbidities. This study showed that previous exposure to a negative stressor, which itself was insufficient to induce depression-like behaviour, could alter epileptogenesis (i.e. the threshold and speed of development of seizures) and predispose a subset of animals to associated comorbidities, including depression-like behaviours and cognitive impairments (Becker C et al. 2015). Notably, this vulnerability to epilepsy and comorbidities (although apparently induced by the same stressor) did not necessarily imply similar mechanisms for each comorbidity, although a cross talk was likely (Bernard C 2016).

Over a lifetime, the "diathesis-epilepsy model" recognises that numerous environmental factors (eg. maternal care, exposure to psychoactive substances etc.) as well as ageing itself may alter gene expression (i.e. the "epigenetic" landscape) feeding back onto the diathesis, and further increasing (or decreasing) vulnerability of individuals (Bernard C 2016).

As a consequence of this research, new evidence suggests that inhibiting BDNF-Tropomyosin receptor kinase B signalling and increase in central levels of neuropeptide Y (NPY) could represent a potential new therapeutic strategy for epilepsy, especially for temporal lobe epilepsy.

Young adults have the highest risk of epilepsy-related deaths

Young adults are at highest risk of premature deaths according to the most recent data from an ongoing Scotland-wide study of mortality in patients with epilepsy who are older than 15 years. During his presentation, Dr Gashirai Mbizvo from the University of Edinburgh revealed that of 2149 epilepsy-related deaths identified in Scotland between 2009 and 2016, young adults (≤ 44 years) and teenagers transferring between child and adult healthcare services were at the highest risk (Mbizvo G et al 2018).

Age-standardised mortality rates (per 100,000 people) were 6.0 (95% CI 2.3-9.7) for 16-24 year olds and 3.7 (1.9-5.6) for young adults between 25-34 years. Overall mortality rates (per 100,000 people) were 6.8 (95% CI 6.0-7.6) in 2009 and increased to 9.1 (95% CI 8.2-9.9) in 2015 Mbizvo G et al 2018).

Sudden Unexpected Death in Epilepsy (SUDEP) accounted for 38% of deaths in adults ≤ 44 years and was most prevalent in Scotland's most deprived areas (Mbizvo G et al 2018). Preventable risk factors for epilepsy-related death identified by researchers included: failure to refer to specialist epilepsy services, lack of patient/care education, drug errors, and delayed specialist review (Mbizvo G et al 2018).

Commenting on these data, a representative from SUDEP Action observed that these finding are consistent with the online Public Health England (PHE) report 'Deaths associated with neurological conditions in England 2001 to 2014' which documented an increase over time in epilepsy-related deaths among people living in England who were at least 20 years old.

However, the circumstances leading to these deaths remain unclear. The ongoing Epilepsy Death Register (EDR) from SUDEP Action aims to provide further insights from bereaved friends and family members into the factors surrounding each epilepsy death (Thomas R et al. 2018).

"Every person who reports an epilepsy-related death helps this research. They bring our knowledge one step closer to finding the answer to SUDEP and other epilepsy related deaths.", Jane Hanna, SUDEP Action Chief Executive.

It is also hoped that the EDR will encourage a closer liaison between professionals and families so that more can be done to identify modifiable risk factors and support those who have suffered a loss. Initial results from the EDR survey, presented at the conference, indicate poor levels of communication and education on the risks associated with epilepsy. More than half of responders of the survey (52.6%) did not know that epilepsy could lead to premature death and 58.1% felt that the circumstances of their loved one's death was not adequately explained (Thomas R et al 2018).

Useful links
https://epilepsydeathsregister.org/
https://sudep.org/

In other news

Dr Pamela Thompson was presented with the annual award for Excellence in Epilepsy by the British Branch of the ILAE. Dr Thompson is consultant clinical neuropsychologist and neuropsychologist lead for epilepsy at the National Hospital for Neurology and Neurosurgery, University College London (UCL) Hospital Trust. She is also head of psychology at The Epilepsy Society. Over the past forty years, she has been responsible for stimulating, designing, coordinating and collaborating on research studies on neuropsychological aspects of epilepsy and has had an academic attachment to the UCL's Department of Clinical and Experimental Epilepsy since its inception. She has co-authored more than 300 research publications and numerous book chapters in addition to literature for people with epilepsy and their families.

Focus on Posters

PAVES identifies vulnerable young people with mental health problems

The Psychology Adding Value Epilepsy Screening (PAVES), conducted in the waiting room at the Royal Hospital for Sick Children in Edinburgh, identified that more than one in three (37%) children and young people with epilepsy (CYPwE) have significant risk of developing mental health problems (George C et al 2018). Early relatively low-level intervention for each of these young people was found to be highly effective in reducing long-term difficulties and pressures on services. Support included psychological self-help literature and referral to existing third sector resources – including psychology/third sector parent workshops and psychology/nurse-specialist led "Psychosocial group Intervention for 12-17 year olds with Epilepsy" (PIE).

"Natural language" algorithm enriches information in patients' records

A "natural language" computer processing technique has been devised by researchers from the Swansea University Medical school to extract detailed clinical information from clinical letters to enrich routinely collected data on epilepsy (Fonferko-Shadrach B et al 2018). Information extracted from the free text in clinical letters accurately identified the type of epilepsy, seizure frequency and neurological investigations which are often missing from patients' records. This automated tool could be used in clinical practice to record patient information in a more structured manner and has the potential to be applied to other diseases.

Basic Science

Real-time measures of post-ictal cortical spreading depression

Cortical spreading depression (CSD) is a dramatic loss of brain ion homeostasis resulting in depolarisation of cortical neurons and astrocytes. CSD is transient and spontaneously reversible, but the mechanisms and consequences of CSD (large-scale changes of local blood flow and metabolism) depend on the circumstances under which the reaction is elicited. The mechanistic links between seizures and sub-cortical CSD is potentially relevant to sudden unexpected death in epilepsy.

During the Basic Science session at the conference, Dr Robert Wykes from University College London, described 3 novel approaches (using in vivo imaging, telemetry devices and grids of graphene transistor arrays) that allow the concurrent recordings of seizures and CSD in awake animals. Using in vivo imaging, Dr Wykes showed that ~25% of seizures evoked in the visual cortex by the administration of GABA antagonist, picrotoxin, were followed by a Ca2+ wave that spread slowly across the cortex followed by electrical silence (Wykes R et al 2018). Interestingly, the depression wave started at a site distinct from the seizure focus and spread radially with no apparent relation to the functional organisation of the cortex (Wykes R et al 2018).

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Epilepsy (Non-US)—The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to seizure medications. AspireSR® and SenTiva™ feature an Automatic Stimulation Mode which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.

Incidence of adverse events following stimulation (>5%) included dysphonia, convulsion,headache, oropharyngeal pain, depression, dysphagia, dyspnea, dyspnea exertional, stress, and vomiting.

Visit www.vnstherapy.com to learn more and view important safety information.

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