TITLE: Predictors of clinically significant anhedonia in refractory epilepsy

Surapi Wijayendran[1*], Rofael Jabr[1*], Lucy Roberts-West[1], Dorothea Bindman[1], Matthew C Walker[1,2], Sallie Baxendale[1], Umesh Vivekananda[1,2**]

* joint first author

** corresponding author: u.vivekananda@ucl.ac.uk, ORCID: 0000-0001-6116-2335

[1] University College London Hospitals Trust, London

[2] Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology

Word count: 1448 words

Tables: 1

Figures: 1

Abstract

Background: Anhedonia, the inability to feel pleasure or motivation for reward, is a core feature of depression in epilepsy, but can occur independent from depression. It is reported in over a third of people with epilepsy and has a significant impact on quality of life. Objectives: This study determined whether specific features of medication refractory epilepsy are predictive of anhedonia. Design: We assessed 267 patients with medication refractory epilepsy for anhedonia, primarily using the clinically validated Snaith-Hamilton Pleasure Scale (SHAPS) scale. Methods: Patients with clinically significant anhedonia were compared with those without for key demographics, epilepsy characteristics and medication using a logistic regression analysis. Results: We found that seizure frequency ($p<0.001$) but not duration of epilepsy was significantly associated with anhedonia. We also found that benzodiazepine use was significantly associated ($p=0.002$) with anhedonia, and levetiracetam/brivaracetam and sodium valproate were significantly negatively associated with anhedonia (0.002 and 0.011 respectively). Conclusion: High seizure burden in medication refractory epilepsy is significantly associated with anhedonia. Specific antiseizure medications are also associated with the development of anhedonia, but it is unclear whether their use is causative or influenced by the presence of anhedonia.

Keywords: Epilepsy, Depression, Anhedonia, Antiseizure medication

Introduction

Depression is the most common comorbid psychiatric disorder in patients with epilepsy with a lifetime prevalence as high as 55%[1]. In addition the risk of suicide is 2.6-5 times higher in patients with epilepsy compared with the general population[2]. Due to the complex and

multidimensional nature of depression, treatment remains challenging. Recent studies have indicated that depression in this group can fail to meet classical criteria, with patients much more likely to report symptoms of fatigue, irritability and anhedonia[3]. Anhedonia is defined as the inability to feel pleasure and a deficit in hedonic experience of rewards or motivation for rewards[4] is a core feature of major depressive disorder[5]. It has a significant impact on quality of life. In recent years, researchers have identified high rates of anhedonia among substantial proportions of individuals with neurological illness such as stroke, dementia and traumatic brain injury[6]. We recently reported that 36% of people with medication refractory epilepsy had clinically significant anhedonia, and whilst these patients were more likely to have a diagnosis of depression, 31% of people without a diagnosis of depression reported significant anhedonia[7]. This is important as population studies have been able to distinguish between anhedonia and depression. Moreover, anhedonia strongly predicts poor treatment outcome of depression[8]. Whether factors specific to epilepsy are associated with anhedonia in this group remains unclear. In this exploratory study, we sought to determine whether particular features of people with medication refractory epilepsy were associated with anhedonia that could benefit from early psychological intervention, and potentially avoid the use of antidepressant medication that can have a negative impact on epilepsy. Since certain antiseizure medications (barbiturates, vigabatrin and topiramate) have significant impacts on mood[9], we also asked whether specific classes of antiseizure medication also had an impact on anhedonia.

Methods

267 consecutive patients with all forms of epilepsy undergoing neuropsychological evaluation were assessed at the National Hospital for Neurology and Neurosurgery, Queen

Square and UCLH Chalfont Centre for Epilepsy, UK, between August 2021 and May 2022. Participants provided written informed consent beforehand and this study was approved by University College Hospitals Trust ethics board as part of service evaluation (ID:37-202122-SE). Patients with a diagnosis of non-epileptic attack disorder were excluded. They underwent a neuropsychiatry review conducted by an experienced neuropsychiatrist as part of routine clinical care, with depression assessed against the Diagnostic and Statistical Manual of Mental Disorders (DSMV) criteria. They were separately assessed for anhedonia using the clinically validated Snaith-Hamilton Pleasure Scale (SHAPS) scale[10], which has a high level of reliability, with convergent and discriminant validity[11]. The SHAPS is a 14-item scale where participants respond to each item along a 4-point Likert scale, covering the ability to experience pleasure in domains of social interaction, food, sensory experience, and interests. Responses of strongly disagree or disagree are given one point, and responses of strongly agree or agree are scored zero points. Each participant's final score ranges from zero to 14, with higher scores indicating higher levels of present state anhedonia. Final scores from the SHAPS were used with a score of 3 or above indicating the presence of clinically abnormal anhedonia and scores of 2 or below reflecting normal levels of hedonic response. The following demographic features of the patients and their epilepsy were drawn from their most recent clinic which was no longer than four months from anhedonia assessment; age, gender, duration of epilepsy, seizure frequency (a rating was assigned: 0 = no seizures for over a year, 1 = yearly, 2 = more than yearly, 3 = monthly, 4 = weekly, 5 = daily), seizure type (focal vs generalised), and current daily medication (Gabapentin/pregabalin; sodium channel inhibitor - lamotrigine, oxcarbazepine, eslicarbazepine, carbamazepine, lacosamide or phenytoin; zonisamide/topiramate, levetiracetam/brivaracetam; benzodiazepine – clobazam or clonazepam; perampanel; valproate).

Statistical/Data analysis

A Pearson Correlation was used for association of anhedonia (0-14 on SHAPS scale as a factor) and depression (0-8 on DSMV criteria as a factor). All the above factors apart from depression were included in a multiple logistic regression analysis as independent variables with anhedonia (yes or no) the dependent variable (performed using SPSS). An odds ratio for presence of anhedonia could then be derived. A subsequent Pearson's correlation was performed comparing seizure frequency with likelihood of anhedonia (number with anhedonia/total number within frequency group).

Results

Of the 267 patients 67% were female, and the median age was 35 years (range 17-82 years). 26% had depression and 44% had anhedonia. These were significantly correlated ($p < 0.001$). We then asked what factors predicted the occurrence of anhedonia using a logistic regression model (table 1). Seizure frequency was strongly associated with anhedonia. In addition, benzodiazepine use was associated with anhedonia whilst use of valproate, and levetiracetam/brivaracetam were negatively associated (Figure 1). This analysis was recapitulated in a linear regression model with SHAPS score as a continuous dependent variable, producing the same results. Increased presence of anhedonia was observed with increasing seizure frequency category (0/1=0.12, 2=0.28, 3=0.52, 4=0.57, 5=0.61). This was confirmed with a significant Pearson's correlation (correlation coefficient 0.33, $p<0.001$).

Table 1: Factors associated with anhedonia

	Odds ratio/year with epilepsy (expB)	*95% CI*	*Uncorrected P value*

Female/Male	1.84	0.93-3.64	0.08
Age	0.99	0.97-1.02	0.95
Duration of Epilepsy	0.99	0.97-1.01	0.37
Seizure Frequency category	**1.86**	**1.45-2.39**	**<0.001**
Epilepsy type (Focal vs generalised)	0.53	0.19-1.45	0.21
Medication			
Sodium channel inhibitor	0.97	0.49-1.91	0.93
Pregabalin/gabapentin	1.35	0.54-3.41	0.52
benzodiazepine	**4.97**	**1.82-13.5**	**0.002**
Levetiracetam/brivaracetam	**0.31**	**0.14-0.66**	**0.002**
Zonisamide/topiramate	0.69	0.25-1.96	0.49
Perampanel	2.93	0.91-8.66	0.07
Valproate	**0.17**	**0.05-0.67**	**0.011**

Discussion

The high prevalence of depression in medication resistant epilepsy has been well established. It is a powerful predictor of quality of life and underdiagnosed in a third of this group [12]. Anhedonia is a principal symptom of depression in epilepsy[3]. In this exploratory study, we further confirmed the high prevalence of anhedonia in people with refractory epilepsy and identified key features predictive of anhedonia. Similar to the findings in depression and suicidal tendency[13], seizure frequency was also significantly associated with anhedonia. The diverse impact of antiepileptic medication was an important finding, namely the strong association of benzodiazepine use and anhedonia, and negative association of levetiracetam/brivaracetam and sodium valproate and anhedonia. Benzodiazepine-use within major depressive disorder has been linked to greater anhedonia levels [14]. In the case of levetiracetam and to a lesser extent brivaracetam, a significant bias may be that these medications were avoided in patients presenting with low mood due to their behavioural side effect profile. The positive effect of valproate cannot be explained by epilepsy type (which was not significant) and is likely to be an effect of medication. Valproate has an existing role as a mood stabilising agent for bipolar disorder. In addition its use in rodent models of

anhedonia appears to exert a protective effect[16]. This study suggests that levetiracetam/brivaracetam and valproate may be protective in patients with medication refractory epilepsy at risk of anhedonia but these findings need confirming in prospective studies, where impact of medication choice can be monitored at multiple time points. Limitations of the study include the absence of prior sample size calculation. Anhedonia assessment was performed at one time point only, and therefore would not capture its fluctuation over time. We were limited to contemporaneous clinical documentation for certain factors such as seizure frequency; although more exact quantification of seizures in a given time period would have been desirable, stratifying over increasing time periods was the best alternative. We did not focus on type of depression if present e.g. mild/major/bipolar depression, as this was outside the scope of the study. Future work would include assessing anhedonia at different timepoints in individuals to understand its dynamic during the course of epilepsy, and the effect of epilepsy surgery on anhedonia.

Conclusion

Anhedonia is a common feature of medication refractory epilepsy that is related to increased seizure frequency and may be influenced by choice of antiseizure medication.

Figure 1. Odds ratio of anhedonia with different antiseizure medications. X axis is a log scale and vertical hashed line denotes an odds ratio of 1.

Disclosures:

Author contributions: SW, RJ, LRW contributed to collection and analysis of data. DB contributed to writing and revising of manuscript. MCW contributed to analysis of data and

writing and revising of manuscript. SB contributed to conception of study and revising of manuscript. UV contributed to conception of study, analysis of data and writing of manuscript.

Funding: This work was funded by the Medical Research Council, Medical Research Foundation, Epilepsy Research UK and University College London Hospitals Biomedical Research Centre.

Competing interests: Declarations of interest: none

References

1. Jackson MJ, Turkington D. Depression and anxiety in epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry* 2005; 76: i45–i47.

2. Christensen J, Vestergaard M, Mortensen PB, et al. Epilepsy and risk of suicide: a population-based case-control study. *Lancet Neurol* 2007; 6: 693–698.

3. Kanner AM. Depression and Epilepsy: A New Perspective on Two Closely Related Disorders. *Epilepsy Curr* 2006; 6: 141–146.

4. American Psychiatric Association (ed). *Diagnostic and statistical manual of mental disorders: DSM-5-TR*. Fifth edition, text revision. Washington, DC: American Psychiatric Association Publishing, 2022.

5. Treadway MT, Bossaller NA, Shelton RC, et al. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J Abnorm Psychol* 2012; 121: 553–558.

6. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci* 2018; 19: 470–484.

7. Roberts-West L, Vivekananda U, Baxendale S. Anhedonia in epilepsy. *Epilepsy Behav* 2022; 108966.

8. Stringaris A, Vidal-Ribas Belil P, Artiges E, et al. The Brain's Response to Reward Anticipation and Depression in Adolescence: Dimensionality, Specificity, and Longitudinal Predictions in a Community-Based Sample. *AJP* 2015; 172: 1215–1223.

9. Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. *Drug Saf* 2007; 30: 555–567.

10. Snaith RP, Hamilton M, Morley S, et al. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry* 1995; 167: 99–103.

11. Franken IHA, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). *J Affect Disord* 2007; 99: 83–89.

12. Boylan LS, Flint LA, Labovitz DL, et al. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* 2004; 62: 258–261.

13. Liu X, Chen H, Zheng X. Effects of seizure frequency, depression and generalized anxiety on suicidal tendency in people with epilepsy. *Epilepsy Res* 2020; 160: 106265.

14. Rizvi SJ, Quilty LC, Sproule BA, et al. Development and validation of the Dimensional Anhedonia Rating Scale (DARS) in a community sample and individuals with major depression. *Psychiatry Research* 2015; 229: 109–119.

15. Chen B, Choi H, Hirsch LJ, et al. Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. *Epilepsy Behav* 2017; 76: 24–31.

16. Goudarzi M, Nahavandi A, Mehrabi S, et al. Valproic acid administration exerts protective effects against stress-related anhedonia in rats. *Journal of Chemical Neuroanatomy* 2020; 105: 101768.