Epilepsy & Behavior Reports 26 (2024) 100658

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Management of anhedonia after epilepsy surgery

Gerardo Maria de Araujo Filho [a], Antonio L. Teixeira [b,c,*]

[a] Department of Neurological Sciences, Psychiatry and Medical Psychology, Faculdade de Medicina de Sao Jose do Rio Preto (FAMERP), São Paulo, Brazil
[b] Faculdade Santa Casa BH, Belo Horizonte, Brazil
[c] Biggs Institute, The University of Texas Health Science Center at San Antonio (UT Health San Antonio), San Antonio, TX, United States

ARTICLE INFO

Keywords:
Anhedonia
Depression
Epilepsy Surgery
Selective Serotonin Reuptake Inhibitor
Temporal Lobe Epilepsy

ABSTRACT

Anhedonia is clinically defined as difficulty or inability to feel pleasure or to be motivated to perform activities that were previously pleasurable. Anhedonia is a core feature of depressive disorders but can be present in other conditions such as substance use and anxiety disorders. Herein we report the case of a 34-year-old female who developed marked anhedonia after left cortico-amygdalohippocampectomy. Despite optimal seizure control, the person struggled with anhedonia and other depressive symptoms. After ruling out medico-neurologic complications, she was prescribed with a selective serotonin reuptake inhibitor and cognitive-behavioral therapy. Anhedonia can be a challenging neuropsychiatric presentation that requires ruling out the effects of antiseizure medications, neurosurgery, and other drugs before prescribing antidepressants.

Illustrative case study

A 34-year-old female came to our clinic with the complaints of "sadness and discouragement for 8 months".

The patient had a history of temporal lobe epilepsy for 18 years with a therapeutic regimen composed of carbamazepine (maximum tolerated dose - MTD: 1,200 mg/day) and phenobarbital (MTD:100 mg/day). Before this therapeutic regimen, she used phenytoin (MTD: 200 mg/day), levetiracetam (MTD: 1,500 mg), and topiramate (MTD: 225 mg/day), all of them in monotherapy. Besides not controlling the seizures, these medications led to meaningful side-effects, respectively, drowsiness, irritability, and cognitive slowness. Since she never had complete control of her focal impaired awareness seizures with pharmacological treatment, she underwent video-EEG and neuroimaging studies which confirmed left mesial temporal sclerosis. She was subjected to cortico-amygdalohippocampectomy for resection of the epileptogenic lesion one year prior to the appointment.

The surgery was successful regarding seizure control, as she had complete remission of seizures (Engel IA) using the same therapeutic regimen (i.e., carbamazepine 1,200 mg/day and phenobarbital 100 mg/day). Prior to the surgery she had one focal seizure per week, with at least one bilateral tonic-clonic seizure per month.

Within three months of the surgery, she developed severe anhedonia characterized by inability to feel any pleasure or to be motivated to perform her usual physical and professional activities. According to her, she "should not have performed the surgery" because "she was able to deal better with the seizures than with the current symptoms", stressing the impact of anhedonia on her routine and duties as a computer technician. In addition, she exhibited low self-esteem with self-deprecating ideas, and sadness with occasional crying spells. She also complained of late insomnia and concentration difficulty. She denied any suicidal ideation and psychotic symptoms.

Of relevance in her past medical history, she had a major depressive episode five years earlier characterized by anhedonia, negative feelings and thoughts along with insomnia. She had a complete remission of symptoms after using sertraline 50 mg/day for one year.

On physical examination, she displayed moderately blunted affect and mild psychomotor slowness, scoring 18 in the Neurologic Disorders Depression Inventory for Epilepsy (NDDI-E). To rule out potential medico-neurologic complications, the patient underwent extensive laboratory workup, EEG, and brain MRI, which were unrevealing.

Based on her medical history, psychopathological signs/symptoms, and the unrevealing laboratory workup, she was diagnosed with moderate recurrent major depressive episode. Given her previous antidepressant response, sertraline 50 mg/day was reintroduced. The patient was also started on cognitive-behavioral therapy (CBT). On follow-up, she had progressive improvement of depressive symptoms. Negative feelings and thoughts improved first followed by insomnia and

* Corresponding author at: The Biggs Institute, the University of Texas Health Science Center at San Antonio, 8300 Floyd Curl Drive, San Antonio, TX 78229, United States.
E-mail address: teixeiraa@uthscsa.edu (A.L. Teixeira).

https://doi.org/10.1016/j.ebr.2024.100658
Received 21 September 2023; Received in revised form 13 February 2024; Accepted 6 March 2024
Available online 7 March 2024

anhedonia, with the patient scoring 6 at the NDDI-E after two months of combined treatment.

Discussion

Clinical signs and symptoms

The presentation of the patient from the clinical vignette is compatible with a full-blown major depression episode in which anhedonia is the most prominent symptom. These symptoms developed after left cortico-amygdalohippocampectomy in a patient with history of mood disorder, factors traditionally associated with an increased risk of neuropsychiatric disorders in epilepsy. Although ASMs, especially phenobarbital, have been related to mood and cognitive symptoms, they played a minor (if any) role in this specific context, as the patient was taking them for many years without side-effects. Conversely, psychosocial factors, especially the patient's struggle to resume her personal and work routine, have probably contributed to her negative self-perception. The fact that the patient improved her anhedonia and other behavioral symptoms with antidepressant treatments supports her main diagnosis of depression, and undermines the possibility of post-neurosurgical apathy or loss of emotional responsiveness, previously reported in the literature as 'neurological athymhormic syndrome' or 'auto-activation deficit syndrome' [1].

In its broader sense, anhedonia is clinically defined as difficulty or inability to feel pleasure and to be motivated to perform activities that were previously pleasurable, for example, going for a walk, chatting with friends, or traveling [1,2]. Accordingly, affective neuroscience studies of reward mechanisms discriminate between 'feeling pleasure' ('liking' or hedonic experience) and 'motivation to perform' ('wanting'). 'Wanting' is generated by large neural systems that include mesolimbic dopamine, while 'liking' is mediated by smaller and functionally fragile neural systems are not dependent on dopamine [3].

Anhedonia is a core feature of depressive disorders, affecting approximately 70 % of these patients [1,2]. However, anhedonia may be present in other neuropsychiatric disorders, such as schizophrenia, anxiety disorders, obsessive–compulsive spectrum disorders, and substance use disorders [1-3]. Anhedonia is also frequent across neurological conditions including Parkinson's disease, Alzheimer's disease, traumatic brain injury and epilepsy, significantly reducing the quality of life of affected patients [3]. In this context, anhedonia has been proposed as a transdiagnostic neurobehavioral syndrome [4,5]. Different medications, such as antipsychotics and anti-seizure medications (ASMs), can cause (or worsen) this condition [2,6].

People with epilepsy (PWE) have higher frequency of anhedonia compared to healthy matched peers [7]. In a recent study, Roberts-West et al. observed elevated levels of anhedonia in 35 % of 211 patients with different epilepsy syndromes, which was associated with the presence of depressive and anxiety symptoms, as well as with cognitive deficits [7]. Depressive and anxiety disorders are among the most frequent comorbidities in PWE [7–9]. Depressive disorders are estimated to have a lifetime prevalence of 30–35 % in PWE [7–9]. Such frequency represents 5.25 times higher than in the general population [10]. Pharmacoresistance, poor seizure control and negative postoperative outcomes are risk factors for the development of depressive and anxiety disorders in PWE [11–13].

Recently, the impact of temporal lobe epilepsy with mesial temporal sclerosis on cognitive processes associated with anhedonia has been investigated. Patients with unilateral mesial temporal sclerosis have impairments in decision-making and reward processes, deficits typically seen in patients with anhedonia [14]. These impairments are possibly related to the disruption of mesial temporal lobe networks that participate in the neural systems underlying 'wanting' [13,14].

Post-surgical neuropsychiatric complications of epilepsy surgery have been recognized for more than 50 years. These complications include: a) a new-onset (*de novo*) psychiatric disorder; b) a recurrence of a psychiatric disorder that had been in remission prior to surgery, like in the current clinical vignette; and/or c) an exacerbation of a psychiatric disorder that was mild in severity and was not recognized by patient, family and/or clinician [11–13]. The most frequent post-surgical neuropsychiatric complications are depressive and anxiety disorders, and more rarely, psychotic disorders and functional seizures (psychogenic non-epileptic seizures) [11–13]. Pre-surgical history of psychiatric disorder (and particularly major depressive disorder, MDD), as reported in the clinical vignette, and persistent seizures after surgery have been pointed out as the main clinical predictors of post-surgical psychiatric disorder [13–18].

Screening for depressive symptoms through self-rating scales

The screening for psychiatric disorders and behavioral symptoms through self-rating scales in PWE occurs in a context of high prevalence of such comorbidities, particularly MDD, and limited access to mental health professionals in both general and specialized health services.

The Beck Depression Inventory (BDI-II) is a commonly used screening instrument for depression [17,18]. It is a self-rating scale that provides severity ranges, as follows: mild depressive symptoms for scores between 14 and 19; moderate, 20–29; and severe, 30 or higher [19–21]. The Patient Health Questionnaire (PHQ-9) is also a self-rating tool useful for screening and serial monitoring of depressive symptoms. These self-rating tools allow the quantification of depressive symptoms but do not control the potential confounding side-effects of antiepileptics that mimic depression (e.g., impaired concentration, sleep disturbance) [19]. For the specific screening of major depressive episode in PWE, the short-structured instrument Neurologic Disorders Depression Inventory for Epilepsy (NDDI-E) [22] was designed and validated. The NDDI-E is a questionnaire with six items, which scores can vary from 1 to 4 in each item (maximum of 24). One of the NDDI-E items is specifically related to anhedonia ("Difficulty in finding pleasure") [22]. The original validation study of the NDDI-E reported that scores >15 are indicative of the presence of major depressive disorder, with a specificity >90 % and a sensitivity 81 % [22]. For higher sensitivity for major depressive disorder screening, lower cutoff scores can be used, and a NDDI-E cutoff score >13 seems optimal for this [23]. Compared to the BDI and PHQ-9, the NDDI-E does not provide a severity score. Moreover, the NDDI-E has just one item to evaluate anhedonia [21,22]. This is a limitation for the specific assessment of anhedonia. Recent studies have used the Snaith-Hamilton Pleasure Scale to specifically evaluate anhedonia in PWE [23,24].

Treatment

The therapeutic approaches for anhedonia have focused on its underlying condition (e.g., depression, anxiety, substance use) to reduce the negative affect and the impairment in motivation and functioning [2,7]. As anhedonia is conceptualized as a core feature of depression, most therapeutic strategies coincide with antidepressant approaches. The treatment for depressive disorders in PWE usually involves pharmacological and non-pharmacological strategies aiming at promoting remission of depressive symptoms and ensuring long-term remission and wellness through the management of psychosocial stressors and socio-occupational reintegration [22].

The patient from the clinical vignette was prescribed selective serotonin reuptake inhibitor (SSRI) sertraline. The main rationale for prescribing this specific instead of other SSRIs, such as citalopram or escitalopram, resides on the patient's previous therapeutic response with this medication. To minimize side-effects of sertraline (e.g., nausea, headache, dry mouth, diarrhea), some argue to start with a lower dose (25 mg). In our case, this was not considered, as the major concern regarding the interaction between sertraline and her ASMs, carbamazepine and phenobarbital, is related to the enhanced metabolization of sertraline, thus reducing its therapeutic effect [23]. The main route of

Table 1
Pharmacokinetic characteristics of antidepressants and potential effects on anti-seizure medications (ASM) [26–30,35].

Antidepressant	Therapeutic dose * (mg/day)	Half-life (h)	CYP450 inhibition	Plasma concentration (ASM)	Plasma concentration (AD) (%)
Fluoxetine	20–60	48–96	1A2, 3A4, 2D6, 2C9, 2B6	PHT: ↑ VPA: ↑	ND
Fluvoxamine	50–250	15	1A2, 3A4, 2D6, 2C9, 2B6		ND
Sertraline	50–250	26	1A2, 3A4, 2C9, 2C19	LTG: ↑ VPA: ↑	CBZ: ↓(21)
Paroxetine	20–60	24	1A2, 3A4, 2D6, 2C9, 2B6	ND	CBZ: ↓(25) PB: ↓(25) PHT: ↓(25)
Citalopram	20–60	33	2D6		CBZ: ↓(31)
Escitalopram	10–20	37	2D6		CBZ: ↓(21)
Duloxetine	30–120	10–15	1A2, 2D6	ND	ND
Venlafaxine	75–300	15–21	1A2, 3A4, 2C9, 2C19	ND	VPA: ↑(27)

ASM: antiseizure medication; AD: antidepressant; *Doses for patients in general; CBZ: carbamazepine; ETX: ethosuximide; LTG: lamotrigine; PB: phenobarbital; PHT: phenytoin; VPA: sodium valproate; ND: no data available.

sertraline clearance is through multiple cytochrome P450 (CYP) hepatic enzymes. Its metabolism is primarily driven by CYP2C9 CYP2C19, CYP3A4, and CYP2D6, with CYP2C19 variants probably having clinical implications (i.e., CYP2C19 poor metabolizers should receive lower starting doses) [23,24]. Carbamazepine and phenobarbital are strong CYP inducers with the potential to accelerate sertraline metabolism [25]. Consequently, many patients taking these ASMs will require higher doses of SSRIs closer to their maximum therapeutic range (200 mg for sertraline) [24–26].

Current recommendations on the pharmacological treatment of depressive disorders in PWE are based on guidelines adopted for the general population, expert opinion, and a few antidepressant trials in epilepsy. The available evidence has favored the use of SSRIs (sertraline, citalopram, escitalopram) and serotonin and norepinephrine reuptake inhibitors SNRIs (venlafaxine, duloxetine) [21,25–33]. The ILAE guidelines have recommended starting antidepressant treatment with low doses and gradual titration up to the minimum effective dose for the remission of symptoms, always monitoring the possible development of adverse effects [21]. Antidepressant treatment should be maintained for at least six months following remission from a first depressive episode, and can be prolonged in cases of residual symptoms. It is worth mentioning that the SSRIs citalopram and escitalopram would be reasonable alternatives in the reported case but were not chosen given the past positive experience of the patient with sertraline. Sertraline, citalopram, and escitalopram are the preferred SSRIs in epilepsy, as they are less potent inhibitors of CYP enzymes compared to other SSRIs (e.g., fluoxetine, paroxetine, fluvoxamine), thus less likely to interfere with ASMs pharmacokinetics. Another antidepressant alternative would be the prescription of the SNRIs, such as starting with a low dose of duloxetine (30 mg) and slowly increasing up to 120 mg depending on the emergence of side-effects (e.g., gastrointestinal symptoms, dizziness) and/or therapeutic response. As antidepressants take two or more weeks to elicit therapeutic response, it is advisable to wait at least two weeks before considering dosage increase. A practical guideline for duloxetine titration is to increase 30 mg every 2 to 4 weeks. Duloxetine is metabolized mainly by CYP1A2 and to a lesser extent by CYP2D6, enzymes that are also induced by carbamazepine and phenobarbital [34]. The use of a different class of antidepressant, such as the SNRIs, is particularly interesting when the patient had failed to respond or had a partial response to a previous trial with a SSRI. In addition to their therapeutic role in depression, SSRIs and SNRIs are effective strategies for the treatment of anxiety disorders that are frequently comorbid with depression in PWE [30–34]. The pharmacokinetic characteristics of the main antidepressants used for PWE, and their interactions with ASM are listed in Table 1 [35]. While antidepressants can increase the plasma concentration of antiseizure medications, the latter can decrease the plasma concentration of antidepressants. The anticonvulsants carbamazepine, phenobarbital, phenytoin, and valproate are potent inducers of CYP enzymes that are also involved in the metabolism of antidepressants.

Table 2
Main effects of anti-seizure medications (ASM) on affective symptoms: [16].

Anti-seizure medication	Mechanism	Main negative effects on affect/ mood	Main positiveeffects
Phenobarbital	GABAergic	Depression, irritability, hyperactivity	–
Clobazam/ Clonazepam	GABAergic	Depression	Anxiolytic, sleep
Phenytoin	?	Depression	–
Valproate*	GABAergic		Mood stabilizer, adjunctive treatment of depression
Carbamazepine*/ Oxcarbazepine	?	Irritability	Mood stabilizer, adjunctive treatment of depression
Vigabatrin	GABAergic	Depression, irritability	–
Tiagabin	GABAergic	Depression, irritability	–
Gabapentin	GABAergic	Irritability, aggression (Children)	Anxiolytic
Pregabalin	GABAergic	–	Anxiolytic
Felbamate	Antiglutamatergic	Anxiety, irritability	–
Lamotrigine*	Antiglutamatergic	Insomnia, agitation, emotional lability	Mood stabilizer, treatment of depression
Topiramate	Mixed	Depression	Impulse control
Levetiracetam	?	Depression, irritability, emotional lability	–
Zonisamide	?	Depression, irritability	–
Perampanel	Antiglutamatergic	Irritability, aggression	

*Approved by the US Food and Drug Administration (FDA) as mood stabilizers.

The psychotropic effects of ASMs are frequently overlooked. ASMs can have positive, negative, or no (neutral) behavioral effects (Table 2) [16]. Several studies have suggested a link between depression and phenobarbital both in adults and in children. The use of primidone has also been associated with irritability and depressive mood [31–35]. Conversely, carbamazepine is a mood stabilizer and sometimes used to potentiate antidepressant treatment. Carbamazepine has been associated with reduced incidence of depressive symptoms in PWE [31–37]. In a large study comparing the behavioral profiles of 18 older and ASM in a

specialty practice-based sample of PWE, the rate of behavioral problems was the lowest with carbamazepine, clobazam, gabapentin, lamotrigine, oxcarbazepine, phenytoin, and valproate [36]. As mentioned in section 2.1, it is unlikely that the ASMs in use have played any role in the patient's presentation. However, tapering off and/or replacing phenobarbital (with lamotrigine, for instance) could be a therapeutic alternative in the context of partial or no response with former measures. Very few studies have specifically investigated the association between ASMs and anhedonia. While levetiracetam use has been associated with increased frequency of anhedonia in PWE, lamotrigine has been implicated in anhedonia improvement [6,38].

In addition to pharmacological management, the patient received CBT. In CBT, the person is guided through structured activities aimed at increasing their awareness of emotions and dysfunctional thought patterns along with the development of coping skills. Although psychotherapies are not easily accessible in many clinical settings, their role in the management of mood disorders should not be understated. Psychological therapies, including CBT, Behavioral Activation and Acceptance and Commitment Therapy, are the first line of treatment for mild to moderate depression in the general population and other chronic health conditions [39,40]. The ILAE recommendations also propose psychotherapy for PWE with mild to moderate depression [21,39,40]. In a randomized study of sertraline versus CBT for depression in PWE, Gilliam et al. found that approximately half of the participants improved their symptoms after 16 weeks, without significant differences in response rate, quality of life, seizures, and adverse treatment effects between the groups [40]. Sertraline and CBT were equally effective, and safe and must be considered taking into account patient's preference. There is evidence that the combination of psychotherapy and antidepressant medication improves clinical outcomes, especially in the long term. The clinical vignette illustrates a very positive and relatively fast outcome when combining both approaches. A major limitation in 'real world' scenarios is the access to evidence-based psychotherapy provided by trained clinicians [21,40].

Referral for psychiatric evaluation should be considered in cases of treatment-resistant depression (i.e., patients who did not achieve clinical improvement after at least two antidepressant trials), depression with psychotic features (e.g., delusions, hallucinations, and gross behavioral disorganization), patients with active suicidal intent, and patients with suspicion of bipolar depression. Patients with history of substance use disorder, previous episode of severe depression, and non-responsiveness to antidepressant treatment are also candidates for psychiatric evaluation and follow-up [21,39,40].

Summary recommendations about the recognition and treatment of Anhedonia in PWE

1. Anhedonia, i.e., difficulty or inability to feel pleasure or to be motivated, can be recognized in PWE, especially those with depressive disorders;
2. Self-report tools (e.g., NDDI-E, PHQ-9) can help in the screening and assessment of anhedonia and other depressive symptoms;
3. Antidepressants, mainly selective serotonin reuptake inhibitors (e.g., sertraline) and serotonin norepinephrine reuptake inhibitors (e.g. duloxetine), are useful pharmacological strategies for the treatment of anhedonia and depression;
4. If anhedonia and depressive symptoms do not respond to first line intervention, the clinician should consider referring to a mental health professional for the implementation of other pharmacological strategies along psychotherapeutic intervention.

CRediT authorship contribution statement

Gerardo Maria de Araujo Filho: Writing – review & editing, Writing – original draft, Conceptualization. **Antonio L. Teixeira:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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