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Treatment of depression in patients with temporal lobe epilepsy: A pilot study of cognitive behavioral therapy vs. selective serotonin reuptake inhibitors☆

Juan Manuel Orjuela-Rojas [a], Iris E. Martínez-Juárez [b,c], Angel Ruiz-Chow [a], Daniel Crail-Melendez [a,c]

[a] Neuropsychiatry Unit, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico
[b] Epilepsy Clinic, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico
[c] Postgraduate Division, Universidad Nacional Autónoma de México, Mexico City, Mexico

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ABSTRACT

There is a high prevalence of depression in patients with epilepsy, which negatively impacts their quality of life (QOL) and seizure control. Currently, the first-line of treatment for depression in patients with epilepsy is based on selective serotonin reuptake inhibitors (SSRIs). The main objective of this pilot study was to compare cognitive behavioral therapy (CBT) versus SSRIs for the treatment of major depressive disorder (MDD) in patients with temporal lobe epilepsy (TLE). Seven patients who received group CBT were compared with eight patients treated with SSRIs. All were diagnosed with MDD and TLE. Patients were assessed at baseline before treatment and at six and 12 weeks during treatment with the Quality of Life in Epilepsy Scale of 31 items (QOLIE 31), the Beck Depression Inventory (BDI), and the Hospital Anxiety and Depression Scale (HADS). Seizure records were also taken on a monthly basis. After 12 weeks of treatment, both groups showed improved QOL and reduced severity of depression symptoms. There were no statistically significant group differences in the final scores for the BDI ($p = 0.40$) and QOLIE 31 ($p = 0.72$), although the effect size on QOL was higher for the group receiving CBT. In conclusion, the present study suggests that both CBT and SSRIs may improve MDD and QOL in patients with TLE. We found no significant outcome differences between both treatment modalities. These findings support further study using a double-blind controlled design to demonstrate the efficacy of CBT and SSRIs in the treatment of MDD and QOL in patients with TLE.

1. Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder associated with epilepsy [1]. In Mexico, 42.7% of patients with epilepsy treated at tertiary centers have symptoms of depression [2], showing a higher prevalence among those with temporal lobe epilepsy (TLE) [3]. Multiple studies have reported negative impacts of depression on QOL and seizure control [4] and increased use of medical services by patients with epilepsy, as well as a rise in costs for caring for those patients [5,6]. Moreover, depression has been associated with higher rates of drug resistance in patients with epilepsy [7]. In fact, it has been suggested that the relationship between epilepsy and depression is bidirectional; having epilepsy would increase the risk of depression, and having depression appears to increase the risk of epilepsy [8,9]. Patients with epilepsy and depression have a high rate of suicide, a situation that underscores the imperative for accurate detection of this comorbidity to provide the best treatments available [10].

The Hermann and Whitman model hypothesizes that the genesis of psychopathology in epilepsy is due to the following three main factors [11]: those *related to the brain*, as in this case, factors with neurobiological characteristics shared by depression and epilepsy [12–14]; those *related to treatment*, i.e., factors caused by depressogenic antiepileptic drugs, such as tiagabine, vigabatrin, topiramate, and phenobarbital [15,16]; and those *unrelated to the brain*, i.e., environmental and psychosocial factors, such as stigma and social discrimination and patients' use of maladaptive strategies (e.g., nonacceptance of the disease) [5,17]. Kanner and Palac agree with this model, stating that depression in epilepsy is often the result of a combination of intrinsic and extrinsic factors that act synergistically [18].

Regarding the treatment of depression in epilepsy, studies suggest that SSRIs are effective, thus, having an antiepileptic effect in addition to an antidepressant effect [19–21]. The 2011 international consensus for the treatment of neuropsychiatric conditions associated with epilepsy suggested that SSRIs are the drugs of choice for the treatment of depressive symptoms in epilepsy [22].

Regarding psychotherapy, Gandy et al. conducted a systematic review on the use of cognitive behavioral therapy (CBT) in patients with depression and epilepsy and found effectiveness in improving

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depressive symptoms when CBT was aimed at improving such symptoms but not seizure control [23].

Despite the aforementioned data and limited evidence on the efficacy of psychopharmacological and psychotherapeutic treatments in this population, there are no published studies specifically focused on the treatment of depression and the improvement of QOL that compare CBT and SSRIs in patients with TLE.

The objectives of this pilot study were threefold: 1) to determine whether comparison between CBT and SSRIs for the treatment of depression in patients with TLE yields proof-of-principle support for conducting a randomized study with a large cohort properly powered to establish efficacy; 2) to evaluate and compare the effects of both interventions on QOL; and 3) to analyze the impacts of both interventions on symptoms of depression, anxiety, and suicidal risk, as well as the frequency of epileptic seizures.

2. Materials and methods

2.1. Patients and procedure

The study was conducted at the National Institute of Neurology and Neurosurgery (NINN) in Mexico City, a highly specialized center to which patients are referred from all over the country. A controlled clinical trial was designed. Participants were recruited from the outpatient clinics of epilepsy, neurology, and neuropsychiatry. Informed consent was obtained from all participants after the procedure had been fully explained. Patients included in the study were greater than 18 years old, of both sexes, diagnosed with MDD according to criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), diagnosed with TLE according to the criteria of the International League Against Epilepsy [24], and were literate. Excluded patients were those with high risk of suicide who required hospitalization; those who abused or were dependent on drugs; those with a history of head trauma within six months prior to the interview; those who had any condition that would prevent them from understanding the study or the psychotherapeutic process, such as mental retardation, psychosis, delirium, or dementia; and those who had previously received CBT. Patients on antidepressant treatments were allowed to participate only if they had been on stable doses for more than eight weeks and still showed signs of significant depression. Participants were eliminated from the study if they failed to complete the scales appropriately, failed to attend at least 80% of CBT sessions, and terminated antidepressant treatment during the course of the study.

We designed and implemented a CBT program to be used in group format that was focused on managing symptoms of depression [25]. One licensed therapist in CBT (DCM) and one companion psychiatrist (JMOR) administered therapy. The certified therapist, who performed as a group leader, had at least 10 years of experience in CBT for depression, and the cotherapist was responsible for overseeing the methodological structure of the sessions. Adherence to the treatment protocol was reviewed after each session.

Of the 25 patients who met the criteria for admission to the study, we achieved telephone contact with only 15 patients. These patients were distributed into two groups. Although group inclusions were initially planned to be randomly assigned, this was not possible because not all patients who met the inclusion criteria were able to attend once-a-week sessions to receive CBT, as they either lived far from the NINN or their economic situation prevented them from attending with such frequency. The groups were, therefore, formed according to the feasibility of being able to attend the weekly sessions.

The first group (n = 7) received 12 CBT sessions consisting of one weekly 90-min session for 12 consecutive weeks. The structure of the CBT is illustrated in Table 1. There were two patients who prematurely discontinued in the CBT group, one patient dropped out after three sessions due to other health problems not related to epilepsy, and the other patient left the group after the eighth session due to severe psychosocial situations unrelated to either epilepsy or depression. Overall, antiepileptic therapy remained stable in most patients who received CBT, except for one patient who changed from valproate to carbamazepine. Two patients were already taking antidepressants (20 mg of fluoxetine for one patient and 40 mg of paroxetine for the other patient) for more than eight weeks but were admitted to the group because they continued having depressive symptoms. The antidepressant medications were not changed for these two patients during the 12 weeks of CBT, and we made sure that no other patient started psychopharmacological treatment during the study period.

Table 1
Cognitive behavioral therapy structure.
Source: D. Crail-Melendez, 2013, Instituto Nacional de Neurología y Neurocirugía, México.

Session 1	Introduction: group rules and CBT presentation
Session 2	To learn the basics of epilepsy and depression, to establish the relationship between mood and seizure control
Session 3	Setting objectives and introduction to the classification system, mood/emotions
Session 4	Modifying activities to improve mood
Session 5	Identification of mood changes, description of the situation and identification of emotion (recording of thoughts)
Session 6	Reviewing thought records, identifying automatic thoughts, finding the evidence
Session 7	Introduction to the list of thought distortions, identifying distortions in the journal
Session 8	Reviewing thought records, learning alternative thoughts, explanation of the concept of unconditional acceptance
Session 9	Introduction to the concept of core beliefs, down arrow technique
Session 10	Obtaining tests, experiments, and plans for problem-solving; coping strategies
Session 11	Integration session: preparation for closure, strategies to prevent relapses
Session 12	Integration session: closure

The second group (n = 8) received treatment with SSRIs (sertraline or citalopram) for a total of 12 weeks. We used the protocol suggested by the American Psychiatric Association (APA) in their practice guidelines for depression [26], in which titration is done at week 6 after the second evaluation according to the study protocol. Initially, we administered sertraline at a dosage of 50 mg q.d. and if there was no response, we increased the dose to 100 mg q.d. Mean doses used were sertraline 75 mg/day (n = 7) and citalopram 20 mg/day (n = 1). Two patients were already taking antidepressants for more than eight weeks but their depressive symptoms persisted in spite of the medication; thus, we decided to optimize their doses at baseline. One patient was lost in this group due to a traffic accident, unrelated to the seizures, which hindered follow-up due to physical disability.

2.2. Measurement

Measurements were performed at three different time points: before starting treatment, and at six and 12 weeks during treatment. A psychologist who was blind to the study and who was trained in the application of the scales used, conducted the measurements at six and 12 weeks. A psychiatrist blind to the study evaluated patients treated with SSRIs and modified or maintained the antidepressant doses according to clinical criteria.

To measure the severity of depression, the Beck Depression Inventory (BDI) was applied, which has been validated in a Mexican population [27]. The BDI has a sensitivity and specificity of 0.86. Severity values determined for a Mexican population are 14–20 = mild to moderate depression and >20 = severe depression.

The Hospital Anxiety and Depression Scale (HADS) was also applied, with its respective subtypes for anxiety (HADS-A) and depression (HADS-D), and with 7 as the cutoff score. The HADS test was designed to assess psychological symptoms of anxiety and depression in patients with other physical illnesses treated in a general hospital, excluding somatic symptoms [28]. The HADS test has also been validated in a Mexican population [29].