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The impact of antidepressants on seizure frequency and depressive and anxiety disorders of patients with epilepsy: Is it worth investigating?

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ABSTRACT

Purpose: Depression and anxiety disorders in patients with epilepsy (PWE) remain under-recognized and under-treated, despite being the most common psychiatric co-morbidities. Selective serotonin re-uptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are considered first-line treatment for primary depression and anxiety disorders. We performed this study to investigate if SSRIs and SNRIs could affect the seizure frequency of PWE and to assess whether such effect is independent of the response of the mood and anxiety disorders to these drugs.

Methods: This was a retrospective study of 100 consecutive PWE who were started on an SSRI or SNRI for the treatment of a depressive and/or anxiety disorder. Every patient underwent a psychiatric evaluation by one of the investigators using a semi-structured interview who also managed the pharmacologic treatment in all the patients. Patients were excluded if they had a diagnosis of psychogenic non-epileptic seizures or if they had undergone epilepsy surgery or the implant of the vagal nerve stimulator six months before and after the start of the antidepressant therapy. The final analysis was conducted in 84 patients. For each type of seizure, an average and maximal monthly seizure frequency during the six months preceding and following the start of psychotropic drugs was extracted from the medical records. We identified the number of patients whose seizure frequency during treatment with antidepressants: (i) shifted from a <1/month to a ≥1 seizure/month and vice-versa, (ii) increased beyond maximal/monthly baseline frequency, and (iii) patients who developed de-novo generalized tonic-clonic (GTC) seizures.

Results: None of the patients with a baseline seizure frequency <1 seizure/month went on to have ≥1 seizure/month after initiating treatment with antidepressants, had an increase in frequency beyond baseline maximal counts or developed de-novo-GTC seizures. Furthermore, there was no seizure recurrence among patients that had been seizure-free. Among the patients with a baseline seizure frequency ≥1/month, 27.5% had a reduction in seizure frequency to <1/month, which suggested a positive effect of SSRI/SNRI on seizure frequency ($p = 0.001$, McNemar test). Among the patients with a baseline seizure frequency ≥1 seizure/month, 48% exhibited a >50% reduction in seizure frequency after the start of treatment with SSRIs or SNRIs.

A therapeutic response to SSRIs and SNRIs was found in 73% of patients. The change in seizure frequency was independent of the improvement in psychiatric symptomatology.

Conclusion: In this retrospective observational study, SSRIs or SNRIs did not appear to worsen seizure frequency. Also, in patients with frequent seizures, SSRIs and SNRIs may be associated with a possible decrease in seizure frequency. Furthermore, these drugs appear to yield good therapeutic response of psychiatric symptoms independently of seizure frequency. It is pivotal to replicate these data in prospective, double-blind, placebo-controlled trials.

1. Introduction

Depression and anxiety disorders are the most common psychiatric co-morbidities in patients with epilepsy (PWE), with a lifetime prevalence ranging from 30% to 35% [1]. These psychiatric comorbidities affect to a very significant degree the lives of these patients such as an increased suicidal risk [2], a poor tolerability of antiepileptic drugs (AEDs), including a predisposition to experience psychiatric adverse events to certain AEDs [3], an association with the development of treatment-resistant epilepsy [4,5], and a poor quality of life [6,7].

Despite their relatively high frequency and significant negative impact in these patients' lives, depression and anxiety disorders remain

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under-recognized and under-treated. For example, previous studies have shown that 30–50% of PWE may be symptomatic for more than one year before any treatment is suggested, irrespective of the severity of the symptoms [8,9]. The long-held misconception that antidepressants have pro-convulsant properties has been one of the most frequent obstacles in the treatment of these conditions. Yet, a review of the literature suggests that most seizures associated with antidepressant drugs have been associated with very high doses, particularly overdoses [10]. In fact, only four antidepressant drugs – maprotyline, amoxapine, chlorimipramine, and bupropion – have associated with the occurrence of seizures at therapeutic doses [10].

Selective serotonin re-uptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are currently considered as first-line treatment for primary depression and anxiety disorders [11]. One study investigated the incidence of seizures in the course of multicenter-randomized, placebo-controlled trials of SSRIs and SNRIs for the treatment of primary major depressive (MDD) and obsessive–compulsive disorders (OCD). Patients randomized to the antidepressant had a significantly lower incidence of seizures than those randomized to placebo [12]. Furthermore, an anticonvulsant effect of these drugs has been suggested in animal models of epilepsy [13], while in patients with treatment-resistant epilepsy, a lower seizure frequency was reported in small open trials with SSRIs including fluoxetine [14] and citalopram [15], although the latter two were open, uncontrolled trials.

To date, there are no class I data on the efficacy of SSRIs and SNRIs in the treatment of depressive and anxiety disorders in PWE, and their use has been accepted by experts' consensus only [16]. Unfortunately, the feasibility of double-blind placebo controlled trials with these drugs in PWE is unlikely as the pharmaceutical industry has shown no interest in making the necessary investments, since these drugs are already available in generic formulation. Furthermore, governmental and non-governmental agencies have failed to support such studies, despite the widespread recognition to obtain such data (e.g., Benchmarks of the National Institutes of Neurologic Disorders and Stroke) [17].

We performed this study to investigate if SSRIs and SNRIs, when used at accepted therapeutic doses, could give a "signal" as to the existence of a positive or negative impact in the seizure frequency of PWE and to assess whether such effect is independent of the response of the mood and anxiety disorders to these drugs. We hypothesized that a positive signal could potentially yield pilot data for a double-blind-placebo controlled trial that could be funded by non-industry sources in the future. The evaluation, selection of SSRI and SNRI, and target doses reflected the recommended and accepted therapeutic strategies followed in clinical practice.

2. Methods

2.1. Patient selection

This was a retrospective study in which 100 consecutive PWE who were started on an SSRI or SNRI for the treatment of a depressive and/or anxiety disorder at the Rush Epilepsy Center of Rush University Medical Center were initially identified. This study was approved by the IRB of Rush University Medical Center.

To be included in the study, patients had to be 18 years or older and have (i) a diagnosis of epilepsy, according to the International League Against Epilepsy classification. (ii) Having symptoms of depression and/or anxiety of at least 2-week duration that have a significant impact on the patients' ability to function normally. Most patients experienced major depressive episodes, generalized anxiety disorder, and an atypical form of depression (e.g., interictal dysphoric disorder) [18]. (iii) Having been on a stable AED regimen for the three months prior to the introduction of SSRIs or SNRIs.

Patients were excluded if they had a diagnosis of psychogenic non-epileptic seizures or if they had undergone epilepsy surgery or the implant of the vagal nerve stimulator six months before and after the start of the antidepressant therapy. Among the 100 patients, 16 patients were excluded; ten patients due to changes in AED regimen or doses in the three months prior the start of antidepressant drugs, and six patients due to having undergone a surgical procedure. The final analysis was conducted in 84 patients.

2.2. Psychiatric evaluation

All patients were evaluated and treated by one of the authors (AMK), who is boarded in Neurology, Epilepsy, and Psychiatry. The evaluation was conducted using a semi-structured interview aimed at identifying any mood and/or anxiety disorder included in the DSM-IV classification as well as any atypical presentation of mood disorders. For each patient, a list of target symptoms was generated. Patients were started at the lowest dose of the chosen antidepressant (see Table 2), which was adjusted if necessary at 4 and 8 weeks after the start of therapy through a telephone contact or at an outpatient visit. The dose was increased until the patient was considered to have reached complete symptom remission or adverse events developed, or the maximal dose was reached, whichever occurred first. In the case of adverse events, the dose was lowered to the previous dose and patients were re-challenged after a two-week period. In case of persistent adverse events, patients were switched to an alternative antidepressant drug. In patients taking an enzyme-inducing AED (e.g., phenytoin, carbamazepine), the final target doses of the SSRI and SNRI were increased by 30% if necessary to adjust for their increased metabolism caused by the AED.

For the purpose of this study, the response of psychiatric symptomatology was recorded at the three- and six-month visits after initiating treatment and were divided into two categories: (i) unchanged, defined as persistence of symptoms and/or frequent symptom recurrence and, (ii) significantly improved, defined as complete symptom remission or occasional recurrence of symptoms which did not affect their level of functioning or did not require further dose adjustments.

2.3. Assessment of seizure frequency

Monthly seizure frequency and type of seizures during the six months preceding and following the start of psychotropic drugs were extracted from the medical records and an average monthly seizure frequency was calculated for these two time periods. Given the natural variation of seizure frequency in patients with treatment-resistant epilepsy, we identified the maximal frequency/month for each patient.

For the purpose of this study, monthly seizure frequency at baseline and during the treatment with antidepressants was categorized into two classes: ≥1 seizure/month and <1 seizure/month. Worsening of seizure frequency was defined as switch from <1 seizure/month to ≥1 seizure/month and/or the development of de-novo generalized toni-clonic (GTC) seizures and/or an increase in seizure frequency beyond the recorded maximal seizure frequency/month. Improvement in seizure frequency was defined as a switch from ≥1 seizure/month to <1 seizure frequency/month.

3. Data analysis

We identified the number of patients whose seizure frequency worsened and improved while on antidepressant therapy according to the definitions cited above. We also calculated the responder rate, defined as the number of patients whose seizure frequency at baseline dropped by >50% during the treatment period with antidepressants among patients with ≥1 seizure/month.

We hypothesized that if antidepressant drugs cause an increase in seizure frequency, there would be a shift from <1 to ≥1 seizure/month categories after the start of the antidepressant medication. Conversely, a shift from ≥1 to <1 seizure/month after the start of antidepressants could signal a possible "positive effect", which could be related to an improvement in mood and/or anxiety symptomatology and/or a possible