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Research paper

What happens to the course of bipolar disorder after electroconvulsive therapy?

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ABSTRACT

Background: Bipolar disorder (BD) encompasses manic and depressive episodes and an illness-free interval. Treatments used in BD patients may influence the ill phases with different actions on the illness-free interval.
Methods: We performed a naturalistic mirror-image retrospective study analyzing the number of episodes and admissions in 41 BD patients for the same period of time of 5 years before and after electroconvulsive therapy (ECT). Furthermore, we assessed the duration of free intervals before and after ECT as a sign of prolonged well-being. Univariate analysis with *t*-test was used to compare differences before and after ECT, while analysis of variance was used to compare factors possibly associated with the efficacy on free-interval of ECT.
Results: Comparing the 5-year periods before and after ECT, we found significantly longer [13.2 ± 9.0 months before ECT to 25.1 ± 19.1 after treatment ($t=3.8$; $p<0.0001$)] free intervals, as well as significant reductions in the number of episodes [5.9 ± 3.0 before ECT to 1.0 ± 1.7 after treatment ($t=9.3$; $p<0.0001$)], and in the number of admissions [2.2 ± 1.3 before ECT to 0.2 ± 0.5 after treatment ($t=9.4$; $p<0.0001$)].
Limitations: The main limitations of this study consisted in the relatively small sample size, the mirror-image retrospective naturalistic study design and possibly patient selection bias.
Conclusions: Electroconvulsive therapy seemed to increase free-intervals and reduced number of BD episodes and admissions. It is plausible that ECT, along with suspending antidepressant treatment, might carry intrinsic stabilizing effect on the course of BD.

1. Introduction

The seminal work of Falret introduced the concept of manic-depressive cycle as the sequence of a manic phase, a depressive phase and an inter-episode illness-free interval with the exception of rapid cycling patients (Sedler, 1983). These three phases are strictly linked and interdependent. Any psychopharmacological therapeutic intervention in the acute phase of bipolar disorder (BD), either hypo/manic or depressive, may impact directly or indirectly on the whole manic-depressive cycle.

Indeed, drugs used in the treatment of the two pathological main phases (depression and mania) might result in an episode of opposite polarity. For instance, antipsychotics can precipitate a depressive syndrome (Kukopulos et al., 1980), while antidepressant drugs may trigger hypomanic or manic episodes (Goodwin and Jamison, 2007; Proudfoot et al., 2011; Saatcioglu et al., 2011; Viktorin et al., 2014) or may accelerate the manic-depressive cycle (Ghaemi et al., 2003; Papolos, 2003). It has been emphasized that the interdependence between depressive and manic phases during the course of BD should be taken into account in treatment-decision making (Koukopoulos, 2006). Furthermore, it has been highlighted the importance of the free-interval as a core component of the manic-depressive cycle which may be modified by mood-stabilizing therapies resulting in prolonged periods of well-being (Koukopoulos, 2006). Typically, however, clinicians tend to focus on the treatment of the two

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morbid phases dedicating less attention to the free-interval.

To our knowledge there is no evidence showing that acute psychopharmacological treatment of mood episodes lengthens the free interval in BD patients, but there is evidence that chronic antidepressant exposure might shorten them (Strejilevich et al., 2011). In a previous study we found that maintenance electroconvulsive therapy (ECT), an effective treatment option in BD (Versiani et al., 2011), lengthened substantially the free interval in rapid cycling BD patients (Minnai et al., 2011). In this current study, we tested whether ECT influenced later illness course in a cohort of 41 non-rapid cycling BD patients who started mood stabilizers and suspended antidepressants. To do so, we evaluated the duration of the free interval comparing the duration of the free interval before ECT with the first interval without illness after the treatment, using a naturalistic mirror-image retrospective design. In addition, we also assessed the number of illness episodes and admissions as well as the modification of the scores at 18-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962; Overall and Gorham, 1988) and Clinical Global Impression Severity (CGIs) scale (Guy, 1976) during the index episode.

2. Methods

2.1. Sample

This naturalistic mirror-image retrospective study was conducted at the psychiatric ward of the San Martino Hospital of Oristano, the reference center for ECT in Sardinia (Minnai et al., 2011; Pinna et al., 2015). We included 41 of the 97 BD patients treated for an acute affective episode with ECT in our unit from 1996 to 2008. Diagnoses of BD were made according to DSM-IV (American Psychiatric Association, 1994). Patients were included if: a) they were able to provide information about the duration of the last illness-free interval and the first after the treatment; b) accurate clinical information on the illness course before ECT and during a follow-up of at least 5 years after ECT was available; and c) there was presence of at least 2 severe affective episodes as well as a clinical course of at least 5 years before ECT treatment. Patients were excluded if: a) they were not affected by BD; b) they had not experienced at least 2 affective episodes before ECT; c) they had not had a clinical course of at least 5 years before ECT; d) they were not able to provide information about the duration of the last illness-free interval and the first after ECT; e) there was no accurate clinical information on the illness course before ECT and during a follow-up of at least 5 years after ECT.

All patients had no psychiatric co-morbidities. The assessment of affective morbidity before ECT was performed through direct interview and a systematic review of patients' medical records. All patients provided informed written consent for ECT, which was performed by trained psychiatrists (GPM, PS). This was a naturalistic retrospective analysis of data collected routinely in clinical settings not requiring an IRB approval. A detailed psychopathological assessment was performed before and after ECT for the index episode using BPRS and CGIs scale. To ensure safety and optimize the effect of ECT we tapered off psychotropic drugs dosages and gradually stopped all the antidepressants during ECT without reinstating them subsequently. The washout period varied for each drug, and, as a general rule, lasted approximately five times the half-life of the specific molecule. Further, we suspended lithium the night before ECT treatment in order to decrease the likelihood of adverse reactions. Efficacy on free-interval of ECT was defined as $>50\%$ reduction of episodes and admissions and $>50\%$ increase in illness-free intervals. All patients had been followed by two authors (GPM, PS) for at least 5 years after the ECT treatment with regular follow-up visits (at least every 6 months).

2.2. ECT treatment

Electroconvulsive therapy was administered using a bidirectional constant current, with brief pulse device. The Thymatron system IV (Somatics, Inc, Lake Bluff, III) was used for 40 patients. Only in 1 case we employed the Mecta Spectrum 5000Q device (Mecta Corp, Lake Oswego, Ore). All patients were treated with bitemporal ECT. For each ECT session we set up: 1) the percent energy determined according to the age of the patient (Abrams, 2002); and 2) the pulse width at 0.5 milliseconds. The other parameters (length of stimulus duration, frequency) were derived automatically by the internal algorithm LOW 0.5 of the Thymatron® System IV. Seizure quality and duration were monitored by a 2-lead electroencephalograph (EEG) and by electromyography (EMG). The ECT was given twice per week for all patients. Propofol (mean dosage 115 ± 50 mg) and succinylcholine (1 mg/kg) for anesthesia and muscle relaxation, respectively, were used during all sessions. ECT was continued until complete recovery from the mood episode was achieved (i.e. resolution of the clinical symptomatology).

2.3. Statistics

We performed univariate analysis with *t*-test to compare differences in number of episodes, of free intervals, and of admissions before and after ECT, as well as for differences in the scores of BPRS and CGIs. Analysis of variance was used to compare factors possibly associated with the efficacy on free-interval of ECT. In particular, sex, onset age and at treatment, diagnosis, type of index episode and onset episodes were compared in responders and non-responders. The significance was set at $\alpha = 0.01$ to account for multiple comparisons and decrease the likelihood of Type 1 error. Variables associated at $p < 0.01$ were inserted into a multivariate analysis model. We did not specify a cut-off for response at BPRS and CGIs since we decided to use them as continuous trait, rather than a dichotomous one, to increase the statistical power able to detect an effect given our small sample size. Statistical analyses employed commercial computer programs (for spreadsheet: *Statview-5®*, SAS Institute, Cary, NC; for analyses: *Stata-12®*, StataCorp, College Station, TX).

3. Results

The diagnosis was BD type I (BD-I) in 25 (61.0%) patients and BD type II (BD-II) in 16. Patients' average age was 46 years and 26 (63.4%) were women. In 19 (46.3%) patients the first lifetime episode was depressive, manic in 10 (24.4%), and mixed in 12 (29.3%) at an average age of 30 years. Nineteen (46.3%) patients were treated for a depressive episode, 8 (19.5%) for mania, and 14 (34.1%) for a mixed state. Patients received an average of 8.39 ECT sessions. Each session had seizure duration recorded by EEG >25 s and by EMG >20 s. The number of ECT sessions ranged between 4 and 20. The mean number of ECT sessions was 9.31, 7.75 and 8.3, for patients who had an index episode of depressive, manic and mixed type, respectively. The clinical characteristics of the sample are detailed in Table 1. Five BD patients (12.3% of the sample) did not have a reduction of affective morbidity in the 5 years after ECT, while the other 36 patients (87.8% of the sample) had a highly significant increase of the duration of the illness-free interval from 13.2 ± 9.0 months before ECT to 25.1 ± 19.1 months after treatment ($t = 3.8$; $p < 0.0001$), with an increase of 36% (Table 2). Moreover, we found a significant reduction of morbidity ($p < 0.0001$) with a drop in the number of episodes of 81%, and in the number of admissions of 90% (Table 2). In addition, the BPRS scores decreased of about 41% and the CGIs score of 64%. The free