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Electroconvulsive Therapy in Bipolar Mixed States: An Overlooked Option

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Mixed affective states are complex presentations of bipolar disorder that represent a diagnostic and therapeutic challenge for clinicians and researchers alike. Treatment guidelines do not usually recommend specific treatments for mixed states, as patients suffering from mixed episodes are generally included as a subsample in trials on acute mania. In clinical practice, mixed presentations in bipolar disorder are largely assumed to have a poorer response to treatment than mood episodes without mixed features.

The present issue of the *Journal* presents a compelling article by Medda and colleagues[1] on the acute use of electroconvulsive therapy (ECT) in a sample of 197 bipolar patients suffering from a severe, drug-resistant mixed state. The sample presented in this study represents a subset of especially difficult-to-treat bipolar patients. Nonetheless, the study clearly suggests that ECT is an effective treatment in mixed conditions, with 82 patients (41.6%) considered responders and 60 patients (30.5%) considered remitters. In the prediction model presented, the authors underline the role of comorbidity with obsessive-compulsive disorder, baseline manic symptom severity, and duration of the current episode as predictors of nonresponse to ECT.[1]

Despite the major limitations of the lack of random allocation of the patients included and the lack of evaluation for rapid-cycling, Medda and colleagues[1] have the merit to provide insight on the clinical management of especially difficult-to-treat patients derived from their tertiary care unit and to focus on a therapy that is often neglected and rarely investigated.

Mixed states represent a well-described clinical feature in the course of bipolar illness. Mixed states have been associated with the use or overuse of antidepressant treatments, which could play a role in their incidence in clinical practice, especially with dual-action serotonin–norepinephrine reuptake inhibitors,[2] and with an increased suicidal risk.[3] The iatrogenic role of antidepressants in mixed states is far from being demonstrated; yet, a recent international consensus agreed on the recommendation to discontinue antidepressants during manic and depressive episodes in patients who present mixed features or who have a tendency to present predominantly mixed states.[4]

In the recent update of the American Psychiatric Association diagnostic criteria (*DSM-5*), the strict criteria for mixed episode have been replaced with episode specifiers that will, as a consequence, increase the prevalence of mixed states in clinical practice,[5] possibly broadening the usefulness of treatment recommendations specifically aimed at mixed states. This update creates an urgent need for more trials that provide separate results for mixed-states subsamples. Given the lack of studies designed to address the efficacy of medications in mixed affective symptoms, guidelines do not fully reflect the current evidence.[6] The situation seems even worse in the case of depression with mixed features, in which the scarcity of researched treatment options often clashes with a clinical management that relies maybe too strongly on antidepressants.

Overcoming the Stigma

Electroconvulsive therapy treatment was introduced in clinical practice by Bini and Cerletti 75 years ago,[7] interestingly, in a case of acute mixed episode. ECT is probably the most controversial practice in psychiatry. The negative public opinion that depicts ECT as an inhuman practice is mirrored by antiscientific beliefs and popular morbid clichés in literature and cinema.

This physical treatment never benefitted from incentive by any trading entity, as it does not offer possibility for patent or economic investment. The lack of financial support, combined with the aforementioned marked stigma, may account for the paucity of clinical research conducted on ECT.[8] Additionally, despite positive results in extremely severe patients, most of whom would never qualify to be enrolled in a drug trial, ECT has received comprehensibly biased treatment in algorithms and clinical guidelines.

Electroconvulsive therapy has undergone, especially in Italy, a long neglect that may recognize ideological and emotional causes, mostly derived from a psychiatric practice aimed more at social containment than health care. Therefore, it seems meritorious that further evidence for ECT effectiveness is now provided by an Italian group. The study by Medda and colleagues[1] adds important insight to the possible use of ECT in mixed states.

Open Questions and Possible Responses

Remission and response rates presented by Medda and colleagues[1] may represent an underestimation of ECT's effectiveness due to the tertiary nature of the unit where the study took place. It is possible that nonresponder rates are not as high as the rates reported in their study (55 individuals, 27.9%). Still, an open question is left to speculation: what to

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do with individuals who prove to be treatment-resistant to multiple pharmacologic options and do not respond to ECT? No treatment algorithm contemplates the management of this subgroup of patients who will typically end up in complex combined treatments. While knowing what to do in such situations is difficult, knowing at least what to avoid can be of help. The prescription of antidepressants in patients with a history of mixed states should be avoided, as this could worsen the course of their illness.[4] When combining treatments, clinicians should address both polarities of the illness while keeping in mind the long-term treatment.[5] The concept of the polarity index of the different treatment options could be of help in the choice of maintenance therapy.[9]

A last issue raised by Medda and colleagues is what to do after the acute treatment with ECT. The same group presented results from a naturalistic follow-up[10] on maintenance treatment with ECT in a small bipolar sample (n = 36), part of which was composed of individuals experiencing a mixed state (n = 17). Electroconvulsive therapy showed a positive impact on the clinical course of severe and treatment-resistant patients with bipolar disorders that presented as a high number of weeks spent in remission during the follow-up period. Evidence on maintenance treatment with nonpharmacologic options in bipolar disorder is scant, but experience in clinical practice seems encouraging. In our tertiary care program,[11] which includes around 700 patients, there are 42 treatment-resistant patients currently showing benefits from maintenance ECT treatment, also on a very long-term follow-up basis. Some patients have been on maintenance ECT treatment (one session monthly) for more than 20 years. In case of treatment-resistant patients, the possibility of synergic, combined pharmacologic-ECT treatment should be considered for maintenance,[10] keeping in mind the possible changes in seizure threshold derived by the different treatment options for bipolar disorder in order to favor those with a minimal impact.[12]

In conclusion, mixed states represent a clinical reality that will possibly increase in prevalence in the near future according to the new diagnostic classification system. Clinicians find themselves with fewer therapeutic options when having to treat patients with mixed features. With this in mind, despite its traditional role as a last-resort-treatment for severe bipolar patients, ECT represents an effective, viable therapeutic option that is probably used too late and not enough, and would benefit from further investigation.

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