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Review article

Clinical and biological predictors of response to electroconvulsive therapy (ECT): a review

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HIGHLIGHTS

- Electroconvulsive treatment (ECT) is a key element of modern psychiatry.
- ECT-responsive patients might be selected a priori on the basis of clinical and biological markers data.
- We indicate some reliable candidate markers for personalized approaches in ECT.

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ABSTRACT

Electroconvulsive therapy (ECT), developed in the 30′s by Bini and Cerletti, remains a key element of the therapeutic armamentarium in psychiatry, particularly for severe and life-threatening psychiatric symptoms. However, despite its well-established clinical efficacy, the prescription of ECT has declined constantly over the years due to concerns over its safety (cognitive side effects) and an increasingly negative public perception. As for other treatments in the field of psychiatry, ECT is well suited to a personalized approach that would increment its efficacy, as well as reducing the impact of side effects. This should be based on the priori identification of sub-populations of patients sharing common clinical and biological features that predict a good response to ECT. In this review we have selectively reviewed the evidence on clinical and biological predictors of ECT response. Clinical features such as an older age, presence of psychotic and melancholic depression, a high severity of suicide behavior, and speed of response, appear to be shared by ECT good responders with depressive symptoms. In mania, a greater severity of the index episode, and a reduction of whole brain cortical blood flow are associated with ECT good response. Biological determinants of ECT response in depressive patients are the presence of pre-treatment hyperconnectivity between key areas of brain circuitry of depression, as well as of reduced glutamine/glutamate levels, particularly in the anterior cingulated cortex (ACC). Furthermore, pre ECT high plasma homovanillic acid (HVA) levels, as well as of tumor necrosis factor (TNF)-α, and low pre-ECT levels of S–100 B protein, appear to predict ECT response. Finally, polymorphisms within the genes encoding for the brain-derived neurotrophic factor (BDNF), the dopamine 2 receptor gene (DRD2), the dopamine receptor 3 gene (DRD3), the cathechol-o-methyltransferase (COMT), the serotonin-transporter (5-HTT), the 5-hydroxytryptamine 2 A receptor (5-HT_{2A}), and the norepinephrine transporter (NET), appear to predict a good response to ECT. The integration of these data in specific treatment algorithm might facilitate a personalized approach in ECT.

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1. Introduction

Since the introduction of electroconvulsive therapy (ECT) into clinical practice by Bini and Cerletti in 1938 [1], a vast number of clinical studies investigated its effectiveness in the treatment of several psychiatric illnesses, creating the evidence-based framework for specific indications and clinical use. International clinical guidelines, such as those formulated by the Canadian Network for Mood and Anxiety Treatments (CANMAT) [2], the American Psychiatric Association (APA) [3], the National Institute for Health and Care Excellence (NICE) [4], and the Royal College of Psychiatrists [5], recommend ECT as first-line option for the treatment of severe, and often life-threatening, psychiatric symptoms. More specifically, CANMAT first-line indications of ECT are acute suicidal ideation, major depressive episode with psychotic feature, treatment resistant depression, catatonia, in cases where a prior favorable response was present, in the presence of repeated medication intolerance, in rapidly deteriorating physical status, during pregnancy (for any of the above indications), and in case of patient choice [2]. According to APA, the principal diagnostic indications for ECT were unipolar or bipolar major depression, mania, and schizophrenia, particularly the catatonic type [3]. In addition, APA supports the primary use of ECT (i.e. prior to a trial of psychotropic medication): 1) whenever there is a need for rapid, definitive response because of the severity of a psychiatric or medical condition, 2) when the risks of other treatments outweigh those of ECT, 3) when there is a history of poor medication response or good ECT response in one or more previous episodes of illness, 4) when ECT is the patient's preference. The NICE guidelines recommend that ECT "is used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening, in individuals with catatonia or a prolonged or severe manic episode" [4]. Finally, the Royal College of Psychiatrists recommends ECT as first-line choice "when there is an urgent need for treatment, for example when the depressive illness is associated with attempted suicide, strong suicidal ideas or plans, life-threatening illness because of refusal of food or fluids" or may be considered "for the treatment of severe depressive illness associated with stupor, marked psychomotor retardation, depressive delusions and/or hallucinations" [5]. In addition, ECT is recommended "if the depressive illness persists with antidepressant treatment". Taken together, these guidelines show a general consensus on the efficacy of ECT: 1) in treating severe depression, particularly when psychotic symptoms and/or treatment resistance to antidepressants and/or suicide ideation is present; 2) for catatonic symptoms; 3) for severe manic episodes. Evidence-based recommendations attempt to establish a framework that can guide clinicians in identifying the most effective, and safe, treatment for a specific patient (i.e. personalized therapy). For instance, treatment algorithms for pregnant bipolar disorder (BD) patients with severe catatonic symptoms indicate ECT as the most appropriate treatment, particularly when benzodiazepine are not effective [5]. Indeed, evidence-based guidelines are formulated on the basis of the available data on the reliability of specific clinical factors in predicting a response to a treatment in a given psychiatric condition. However, most of these recommendations do not take into account data on biological predictors, such as, for instance, genetic markers, which, if analyzed jointly with clinical data, might ultimately lead to accurate prediction of response and personalized treatment [6]. In this context, we aim to selectively review the evidence on clinical and biological predictors of a response to ECT. Since a systematic assessment of the pertinent literature lies outside the scope of this review, we refer the readers to recently published estimates of the predictive power of clinical factors in influencing a response to ECT in depressive subjects [7]. Instead, we aim to present an overview of the clinical and biological factors appearing to modulate a response to ECT. Specifically, we will first quantify the clinical effectiveness of ECT, particularly in the treatment of depression. Further, we will perform an historical overview of ECT, as well as summarize the main electrophysiological principles of ECT. The core of our work will review the data on the most relevant clinical and biological predictors, including functional Magnetic Resonance Imaging (fMRI), of a response to ECT in mood disorders (MD). Finally, we will present a perspective on the possible implication of imple-

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