Personalized Medicine in Psychiatry 17–18 (2019) 23–31

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.elsevier.com/locate/pmip

Precision ECT for major depressive disorder: A review of clinical factors, laboratory, and physiologic biomarkers as predictors of response and remission

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ARTICLE INFO

Keywords:
Precision ECT
ECT
Predictors of response
Predictors of remission
Depression
Major depressive disorder

ABSTRACT

Predicting which patient(s) will respond to Electroconvulsive Therapy (ECT) has very important clinical implications. The aim of this manuscript is to review the current literature on clinical, physiologic and laboratory biomarkers as predictors of ECT response and remission related to the treatment of major depressive disorder (MDD). We will briefly discuss available research on the predictors of cognitive side effects of ECT. Although each clinical factor may have subtle influence on ECT response, taken together clinical predictors can lead to a robust treatment plan tailored for an individual patient, and advise on the likelihood of ECT response. Available literature supports the predictive value of several clinical factors. Older age, psychotic depression, and depression severity positively predict ECT response. Limited data is available for catatonia specific to MDD, but overall data shows positive response of ECT for the treatment of catatonia. Multiple medication trials in the current episode and comorbid psychiatric diagnosis (including borderline personality disorder and substance use disorder) predict lower response.

Lack of widespread clinical availability and validation in larger studies limits current clinical utility of laboratory and physiologic biomarkers. Genetic, epigenetic, and proteomic factors have been investigated predominately in animal models, but ongoing research in human studies including neuroimaging is promising. Thus, these biomarkers provide an exciting outlook that may elevate the precision of ECT response and remission.

1. Introduction

Electroconvulsive Therapy (ECT) effectively treats a broad spectrum of severe psychiatric illnesses including major depressive disorder (MDD), bipolar disorder, schizophrenia, and catatonia. Given the cost and limited accessibility of ECT, predicting which patients will respond to ECT has very important clinical implications. The most common indication for ECT in the United States is MDD. Thus, in this manuscript, we will review clinical predictors and biomarkers of ECT response and remission in the treatment of MDD. We will also discuss available research on the predictors of cognitive side effects of ECT.

The form of ECT delivered in individual studies may shape the interpretation of each predictive variable. While an exhaustive discussion of ECT technique is beyond the scope of this paper, the reader should be aware that higher doses of electrical stimulation and bilateral (BL) electrode placement can generally be associated with greater and/or faster antidepressant efficacy as compared with lower dose stimulation and right unilateral (RUL) stimulating electrode placement [1]. Although each clinical factor may have subtle influence on ECT response, this review aims to provide a broad overview of clinical predictors in MDD, which taken together can form a robust treatment plan tailored for an individual patient, and advise on the likelihood of ECT treatment success. Predictors of ECT response and remission as supported by Meta-analysis are presented in Table 1. Summary of studies supporting predictors of response and remission of ECT are presented in Table 2.

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https://doi.org/10.1016/j.pmip.2019.07.001

Table 1
Predictors of ECT response and remission as supported by Meta-analysis.

Predictor	Authors/year	Studies included	N	Finding
Age	Haq et al. [3]	10	702	Older age is positive predictor of efficacy
	van Diermen et al. [2]	24 (remission)	2863	
		25 (response)	2633	
	Haq et al. [3]	5	302	Age at onset not significant
Depressive episode severity	van Diermen et al. [2]	23 (remission)	2531	Positive predictor of response, not remission
		26 (response)	2663	
	Haq et al. [3]	9	523	Not significant
Duration of current episode	Haq et al. [3]	7	702	Shorter episode predicts response
Medication failure	Haq et al. [3]	11	1175	Medication treatment failure in current episode predicts lower response rate
Melancholia	Haq et al. [3]	5	946	Inconclusive due to heterogeneity of studies and differing definitions of melancholia
	van Diermen et al. [2]	7 (remission)	1242	
		5 (response)	524	
Psychotic depression	Haq et al. [3]	17	2328	Psychosis is a positive predictor of efficacy
	van Diermen et al. [2]	21 (remission)	2787	
		21 (response)	2396	
Gender	Haq et al. [3]	11	1796	Not significant
Number of previous depressive episodes	Haq et al. [3]	5	332	Not significant

Haq et al. found studies by performing a PubMed literature search with the terms "electroconvulsive therapy, predictor, depression, and response" along with 15 terms for their target clinical predictors and selecting studies published after 1980. Studies were further required to have published data sufficient to calculate effect size and report outcome as a dichotomous variable. A total of 32 studies were included and 19 were excluded due to not reported, incompatible outcome measure, or insufficient data published. Main limitations of this meta-analysis include missed studies, studies that did not meet inclusion criteria because of insufficient published data, data incompatible with meta-analysis, lack representation for individuals with severe mental illness, and most data was sourced from academia in North American and Europe.
van Dierman et al. included studies that met the following criteria: published in English after 1995, conducted on adults with unipolar or bipolar depression, confirmed psychotic or melancholic symptoms by structured diagnostic or clinical interview, classified response/remission based on Hamilton Rating Scale for Depression or Mongomery-Asberd Depression Rating Scale, and provided data sufficient to calculate effect sizes. Main limitations include large studies that were excluded based on criteria, studies that did not provide sufficient data, significant heterogeneity between included studies, and the exclusion of studies using ultrabrief-pulse ECT.

2. Demographics

2.1. Age

2.1.1. Age at time of treatment

Older age has been demonstrated to be a positive predictor of remission and response in two independent meta-analyses. van Dierman et al. 2018 calculated that the standardized mean difference (SMD) for remission was 0.26 across 24 separate studies, and SMD for response was 0.35 across 25 separate studies ($p < 0.001$). A quantitative analysis revealed that the absolute age difference between those who did remit (average age 59.7 years) versus who did not remit (average age 55.4 years) was 4.3 years. There were several main sources of heterogeneity that affected the influence of age regarding both response and remission rates. First, a longer length of duration of the current depressive episode yielded greater SMDs. Additionally, older age was more strongly predictive when using electrode placement in the right unilateral as opposed to only using a bilateral placement [2].

A review by Haq et al. also found older age to significantly predict a favorable treatment response [3]; however, the authors express some doubt of the true accuracy of that estimate given the heterogeneity of the included studies.

Kellner et al. categorized age into two groups, the first group being patients aged 60–69 and the second being patients aged 70 and above. All patients in this study received RUL ECT. Patients belonging to the more senior group were 1.89 times more likely to remit than those in the less senior group, 69.7% of the most senior demographic remitting as compared to 55% of patients in the less senior demographic [4]. Based on this study, response appears to favor older patients, especially the old-old.

2.1.2. Age of onset of major depressive disorder

Age of onset was not a significant predictor of treatment response in an analysis that reviewed 5 studies reporting this data [3].

2.2. Race/ethnicity

ECT has been shown to be disproportionately underutilized in ethnic minorities including African Americans, Latinos, and Asian Americans [5]. This disparity persists even after controlling for potential confounding factors such as age, insurance coverage, socioeconomic status, disease severity, and readmission rates [6]. Given this inequality, there is a corresponding scarcity of literature pertaining to ethnic considerations in ECT.

Williams et al 2008 was the first to study treatment outcomes in African American patients versus white patients undergoing BL ECT for MDD [7]. In this study, 483 (94%) patients were white, and only 32 (6%) patients were black, which is indicative of the imbalanced treatment population overall and possibly limits statistical power for comparison between racial/ethnic groups. At baseline, black patients who were referred and ultimately enrolled in the study had experienced fewer total episodes of depression, were rated to have more severe depression, experienced more psychotic features, and were less likely to have demonstrated medication resistance through adequate trials prior to ECT. Overall, outcomes between races were not significantly different as measured by remission rates, dropout rates, and improvement in depression rating severity.

One case series examined treatment outcomes for Chinese patients receiving ECT for both mood and psychotic disorders in New York City [8]. A total of 12 cases using mixed electrode placements were reported. No major differences in outcome were observed in comparison to larger American or Asian data sets as measured by the average number of treatments administered, response rate, and relapse rate. As in the prior study of ECT in African Americans, in this study, Chinese Americans were highly likely to have psychotic depression, as all these patients with affective disorders had delusions.

There is evidence that there are racial differences in the symptoms prompting ECT referral and that racial minorities are less likely to receive evidence-based practices both before consideration for ECT and during the course of ECT itself [7,9]. It is also critical to note that although multiple separate studies observed that minority patients

Table 2
Summary of studies supporting predictors of response and remission of ECT.

Predictor of ECT response	Authors/year	Findings
Demographics	Haq et al. [3]	older age predicts response
		age at onset is not significant
		Gender is not significant
	Kellner et al. [4]	old-old(> 70) predicts response more than young-old (60–69)
		Gender is not significant
	Williams et al. [7]	African American is not significant predictor
	Fox et al. [8]	Chinese is not significant predictor
SES	Bennet et al. [10]	Socioeconomic status does not affect outcomes, in Scotland
	Kellner et al. [4]	education level is not a significant predictor
Melancholia	Coryell and Zimmerman [20]	melancholia does not predict outcome
	Kellner et al. [4]	melancholia does not predict outcome
	Tsuchiyama et al. [15]	melancholia does not predict outcome
	Haq et al. [3]	melancholia inconclusive predictor
	van Diermen et al. [2]	melancholia inconclusive predictor
	Pinna et al. [11]	melancholia inconclusive predictor
	Sivaprakash et al. [21]	melancholia with diurnal mood variation predicts response
	Gupta et al. [22]	melancholia with SI and poor appetite predicts response
Depression with psychotic features	Haq et al. [3]	psychosis predicts response
	Pinna et al. [11]	psychosis predicts response
	Petrides et al. [27]	Psychosis predicts more likely and faster response
	van Diermen et al. [2]	psychosis predicts response (OR 1.69) and remission (OR 1.47)
	Kinder et al. [23]	psychosis is not significant predictor
	Lam et al. [24]	psychosis is not significant predictor
	Kellner et al. [4]	psychosis is not significant predictor
	Tsuchiyama et al. [15]	psychosis is not significant predictor
	Okazaki et al. [18]	psychosis is not significant predictor
	de Vreede et al. [25]	psychosis predicts non-response
	Birkenhager et al. [26]	delusions predict response
	Buchan et al. [14]	delusions predict response
	Sivaprakash et al. [21]	delusions predict response
	O'Leary et al. [13]	delusions not significant predictor
MADRS	Okazaki et al. [18]	High Factor 1 score predicts response. Higher Factor 3 scores predict delayed response time.
Suicidal Ideation	Kellner et al. [4]	No suicidality predicts response (OR 2). RUL electrodes
	Pinna et al. [11]	High expressed SI predicts response. BL electrodes
Polysomnography	Goder et al. [51]	First REM period density predicts response
Psychomotor disturbance	Pande et al. [12]	Psychomotor agitation correlated with non-response. Electrode placement not specified
	O'Leary et al. [13]	Psychomotor not significant. Randomized RUL vs BL electrode
	Buchan et al. [14]	Psychomotor depression predicts response. BL electrodes.
	Tsuchiyama et al. [15]	Psychomotor agitation or depression is insignificant. Electrodes not specified.
Cognition	Bjolseth et al. [17]	baseline cognition does not predict outcome
Depression Severity	van Diermen et al. [2]	high depression severity predicts non-remission
	Pinna et al. [11]	high severity predicts response
		longer index episode duration predicts non-response
	Haq et al. [3]	severity is not significant
		longer index episode duration predicts non-response
		Treatment resistant depression has lower response rate (58 vs 70%)
	Kellner et al. [4]	severity is not significant predictor of remission
		Number of hospitalizations does not affect remission
	Dombrovski et al. [19]	depression > 2 yrs predicts non-remission
Genetics	Minelli et al. [36]	GRIK4 polymorphisms predict response
	Benson-Martin et al. [37]	COMT polymorphisms predict response.
		Dopamine D2 and D3 receptor polymorphisms predict response and remission.
		TPH1, 5-HTTLPR ll coupled with NET polymorphisms predict poorer response
		BDNF polymorphism predicts response
	Sutton et al. [38]	APOE-ε4 predicted response in one study, but not replicated in other larger studies
Epigenetics	Kleimann et al. [39]	Decreased Methylation at BDNF promotor predicts response
Proteomic	Ryan et al. [40]	PEDF increases following ECT but does not significantly predict clinical outcome
Endocrine	Vukadin et al. [41]	post dexamethasone cortisone non suppression predicts response
Neuroimaging	Oltedal et al. [43]	ECT induces structural volume changes, but predictive models limited by power
	Redlich et al. [44]	Machine learning predicted ECT response with 78% accuracy base on pre ECT MRI
	van Waarde et al. [46]	Machine learning based on resting state fMRI predicts response with PPV of 80% and 88%
	Jiang et al. [45]	Machine learning based on pre ECT structural MRI and several gray matter areas predicted response with 86%, 89%, and 90% accuracy
	Leaver et al. [47]	Machine learning based on fronto-temporal connectivity predicts response with a balanced accuracy of 58–68%
EEG		pre-ECT cingulate cortex theta cordance predicts response
Comorbid psychiatric diagnosis	DeBattista and Mueller [32]	Borderline PD predicts poorer response
	Feske et al. [31]	Borderline PD predicts poorer response
	Rasmussen [30]	Borderline PD predicts poorer response
	van Waarde et al. [33]	ECT effective in comorbid Mental retardation, but limited data
Predictors of Cognitive side effects		
Baseline cognition	Dybedal et al. [53]	Baseline cognition (in patients without dementia) does not affect cognitive side effect risk. Randomized BF vs RUL
	Hausner et al. [54]	lower baseline cognition predicts transient cognitive decrease.

(*continued on next page*)

Table 2 (*continued*)

Predictor of ECT response	Authors/year	Findings
Age	Semkovska et al. [55]	Older age predicts acute decrease in executive function 3 days post ECT, no effect at later time points.
Parkinson's	Oh et al. [56]	Patients with Parkinson's may have increased risk of post ECT delirium
	Borisovskaya et al. [57]	inconclusive cognitive outcomes

receiving ECT were more likely to have psychotic features [7–9], psychosis is not a specific indicator for ECT referral for minority patients per se. Given that there is no current data to suggest differing treatment outcomes for racial minorities, it is important to remain cognizant that all ethnicities should be considered for ECT with equal prevalence and symptom severity. Future research is needed to explore the role that culture, stigma, and bias serve as barriers to minorities consenting to treatment even after they are referred.

2.3. Gender/socioeconomic status/education/family history

2.3.1. Gender

Data from 11 separate studies was reviewed in a 2015 meta-analysis that did not find any significant effect of gender on treatment response [3]. Additional data from a large, multisite study by Kellner et al did not find a clinical correlate for gender either [4].

2.3.2. Socioeconomic status

A Scottish study that compared socioeconomic status and ECT outcomes found no significant differences in the number of treatments received or the total reduction of depression severity rating amongst varying levels of SES [10]. More research is needed in order to generalize this finding to the United States, given the different insurance and accessibility landscape.

2.3.3. Education

One study was found that examined years of education and outcomes. Education was not a significant predictor of treatment response [4].

2.3.4. Family history

In the Kellner et al. 2016 Prolonged Remission in Depressed Elderly (PRIDE) study, family history of psychiatric illness, mood disorder, MDD, or bipolar disorder did not predict treatment response [4].

2.3.5. Demographics summary

Though various demographic factors have been studied, only age at time of treatment appears to have evidence for predicting ECT response (older age correlated positively with treatment response). The role of race/ethnicity is unknown, but the lack of data highlights overall disparities in access to ECT. Age at onset of depression, gender, socioeconomic status, level of education, and family history are not significant predictors.

3. Clinical factors

3.1. Specific depression characteristics

3.1.1. Suicidal ideation

In the PRIDE study, patients with no suicidality, assessed by a score of 0 on the Beck Scale for Suicide Ideation, were twice as likely to remit with RUL ECT when compared to those with scores > 0 (OR = 2, p = 0.02) [4]. This conflicts with finding from a 2018 narrative review which looked at 2 studies examining suicidality and concluded that depressed patients with high expressed suicidal ideation have better response to ECT [11]; however both of these studies utilized BL electrode placement.

3.1.2. Psychomotor disturbance

In a study of 48 depressed inpatients, Pande et al. found that non–responders to ECT had significantly higher initial psychomotor agitation; however, electrode placement was not specified [12]. In contrast, in the Nottingham ECT trial, baseline psychomotor agitation in depressed patients (n = 13) did not predict ECT response when patients were randomized to RUL vs BL electrode placement [13]. The Leicester and Northwick Park trials (n = 70) found better BL ECT response in depressed patient with psychomotor retardation, especially in those who had delusions [14]. This conflicts with Tsuchiyama et al.'s prospective study of 24 inpatients which did not find an association between response to ECT and baseline psychomotor agitation or retardation, but electrode placement was not reported [15]. The conflicting findings may be explained in part by the heterogeneity in ECT methods.

3.1.3. Cognition

One study looked at overgeneral memory (OGM), measured using the Autobiographical Memory Test, as a possible predictor of ECT outcomes in 25 depressed patients. OGM is an inability to retrieve specific memories from one's autobiographical memory. Instead, general memories are recalled, such as repeated events or events occurring over broad periods. This cognitive phenomenon is linked to depression. Raes et al. randomly assigned subjects to bifrontal or RUL ECT and found that though baseline OGM was unable to directly predict immediate post-ECT outcome, it did show that an increase in depressive symptoms 1 week after cessation of ECT was highly correlated to high baseline OGM. This held true even in responders to ECT. However, the sample size was small and follow up was only done at 1-week post-treatment which precludes from drawing firm conclusions. This suggests that OGM will need to be studied with larger studies to further investigate its utility in predicting response to ECT [16].

In another study, baseline cognition was assessed in 65 depressed elderly patients using 9 neuropsychological tests examining information processing speed, memory, executive function and verbal learning. Patients were randomized to BF and RUL ECT and were reassessed during the ECT course and 4 days after the last session. Twenty-seven of these patients showed mild cognitive impairment at baseline and 55.6% of those no longer met criteria for mild cognitive impairment (MCI) post ECT. However, overall, they found that these specific baseline cognitive parameters did not predict ECT remission, suggesting no difference in treatment response in elderly patients with MCI vs no MCI [17].

3.1.4. Depression severity

Some literature on ECT remission indicates that depression severity is a predictor of remission/response to ECT, while others do not. Some evidence suggests that remission was less likely in patients with higher depression severity scores [2]. Other reviewers have found that greater severity at baseline can indicate a good response to ECT [11]. A meta-analysis by Haq et al. found that severity of depressive symptoms overall was not a predictor although there appears to be a lot of heterogeneity in the literature [3]. This finding is consistent with the more recent PRIDE study, in which severity ratings on the HAM-D Rating Scale, Clinical Global Impressions Severity, and Cumulative Illness Rating Scale for geriatrics, were not predictors of remission [4].

In a prospective study of 24 inpatients, Okazaki et al investigated if the 3-factor model of the Montgomery and Asberg Depression Rating

Scale (MADRS) could predict ECT response with BL electrode placement. They concluded that higher baseline factor 1 scores, representing dysphoria (sadness, pessimistic thoughts and suicidal ideation), predicted better ECT response. They also found that patients who showed response 1 week after ECT had higher baseline factor 3 scores, representing vegetative symptoms (reduced sleep, appetite, and inner tension), when compared to non-responders, suggesting delayed response time [18].

Meta-analysis [3] and review [11] have shown that longer index episode duration correlates with a poorer response to ECT. Another study found that chronicity, defined as depression lasting longer than 2 years, was a stronger predictor of non-remission than single episode duration [19]. The number of prior depressive episodes [2,3] and prior psychiatric hospitalizations [4] have not been found to be a predictor of ECT efficacy.

3.1.5. Treatment resistance

In the United States, ECT is commonly used as a secondary treatment after first-line pharmacotherapy (or after several lines of treatment) has failed. In the literature, there does not appear to be clear acceptance of how many medications should be tried before ECT is considered, but currently patients referred for ECT are those that need rapid treatment response, often in the context of multiple failed antidepressant trials. Treatment resistance is a robust factor that affects ECT response. One meta-analysis found a response rate of 58% for patients with treatment-resistant depression and 70% for those without [3].

3.1.6. Summary of specific depression characteristic findings

Suicidal ideation predicts poorer response to RUL ECT and better response to BL ECT in separate studies. Data conflicts on psychomotor disturbance as a predictive factor. Baseline cognition does not appear to predict remission. Meta-analyses show that depression severity does not predict remission but may predict response. Medication failure predicts lower rate of response.

3.2. Depression subtypes

3.2.1. Melancholic depression

Evidence about the utility of melancholic features as predictors of ECT has been mostly inconclusive. Melancholia was found to have no predictive value on outcomes in a 1984, naturalistic, study of depressed patients where RUL ECT was used [20]. This was also the case in the PRIDE study [4]. Similarly, a prospective study of 24 inpatients found that baseline melancholia was not a statistically significant predictor of outcome [15].

The evidence of melancholic depression as a predictor of ECT was also explored in 2 meta-analyses [2,3] and 1 narrative review [11]. They found that melancholic depression did not significantly predict ECT outcomes; however, these results were deemed inconclusive due to the heterogeneity of the included studies, different definitions of melancholia between studies and the small number of studies.

Some researchers argue that the indefinite evidence is due to the use of different definitions of melancholia. Thus, some investigated specific symptoms of melancholia rather than it as a subtype of depression. In one prospective study of 30 depressed patients, they found that diurnal variations of mood, seen in melancholic patients, were significantly associated with better response to ECT ($p = 0.034$) [21]. Another prospective study of 22 patients with endogenous (melancholic) depression found that suicidal ideation ($p < 0.005$) and poor appetite ($p < 0.01$) predicted good response to ECT [22].

3.2.2. Depression with psychotic features

Psychotic depression is often studied as a clinical predictor of ECT response. Retrospective chart reviews showed conflicting results; a review of 52 depressed patients, who received BL ECT, found no significant difference between responders and non-responders with regards to psychosis [23]. Similarly, a retrospective chart review of 174 patients found that psychotic depression was not a significant predictor of ECT response, where 45% of patients received RUL ECT, 35% BL, and 20% received both RUL and BL [24]. Another review of 53 depressed patients treated with BL ECT identified psychotic depression as a negative predictor of ECT response [25]. This conflicted with another retrospective study of 55 inpatients which found delusional depression had superior response to ECT than the non-delusional depressed ($p = 0.002$), after 19 patients received RUL ECT, 17 patient received BL ECT and 19 patients were transitioned from RUL to BL ECT [26].

Prospective studies also showed conflicting results; a multisite NIMH study of 77 patients with psychotic depression and 176 patients with nonpsychotic depression using BL ECT found that patients with psychosis were more likely to remit and more quickly than those without psychosis [27]. The Leicester and Northwick Park trials found better response to ECT in depressed patients with delusions [14]. This concurred with another prospective study of 30 patients, who received BL ECT, that found the presence of delusions in depressed patient to predict favorable ECT response ($p = 0.005$) [21]. The Nottingham ECT trial found no significant difference in response rates to ECT in depressed patients with baseline delusions ($n = 12$) [13]. In the PRIDE study, baseline psychotic depression was present in 71.4% of remitters after an acute course of right unilateral ultra-brief pulse ECT, yet it was again not a statistically significant predictor (OR = 1.64 $p = 0.262$) [4]. Similarly, Tsuchiyama et al. and Okazaki et al. found that psychotic depression did not predict response to ECT [15,18].

Despite the conflicting evidence, reviews indicate that psychotic depression maybe a favorable clinical predictor of ECT outcomes. A 2015 meta-analysis of 17 studies found that psychotic symptoms were associated with better response to ECT, however, they reported that this finding was weak due to significant study heterogeneity [3]. A narrative review of 5 studies, including 2 RCTs, concluded that psychotic depression positively predicted ECT response [11]. Finally, a 2018 meta-analysis of 21 studies found that patients with psychotic depression had superior ECT remission (OR = 1.47, $p = 0.001$) and response (OR = 1.69, $P < 0.001$) [2]. Furthermore, in the remission heterogeneity analysis, they found that this predictive effect of psychosis was stronger in older patients and in patients with lower levels of medication resistance. In the response analysis, ECT course length was a clinical source of heterogeneity, with longer courses significantly corresponding to psychotic depression being a stronger predictor of ECT response [2]. The clinical decision to terminate an acute course of ECT for psychotic depression needs to be weighed with the consideration that a longer course of ECT may improve benefit.

3.2.3. Depression with catatonia

Current evidence indicates that ECT is effective for treating catatonia in general, with a response rate ranging from 80 to 100% [28,29]. However, data pertaining to the use of ECT in patients with catatonia due to MDD remains limited.

3.2.4. Summary of depression subtype findings

Melancholia has been extensively reported as a potential predictor, but data is inconclusive due to heterogeneity in study methods and definitions of melancholia. Psychotic features predict treatment response, as evidenced by meta-analyses and multiple studies.

3.3. Comorbid psychiatric disorders

3.3.1. Personality disorders

The largest amount of research into the use of ECT for personality disorders (PD) has focused on those with borderline personality disorder (BPD). While research in this area is still limited, the predominance of the data indicates ECT has decreased efficacy in this population [30–32]. A 2001 review of the literature found that those with BPD have lower magnitude of response as measured by Beck

Depression Inventory, lower response rates, and higher rates of relapse [32]. ECT can be beneficial for mood components of personality disorders, though there is not much support that ECT improves other dimensions of personality disorders.

3.3.2. Intellectual disability

ECT has been shown to be safe and effective for patients with MDD and comorbid intellectual disability; however, research in this population is limited. A review of 44 case studies of patients with depression and intellectual disability found that ECT was 87% effective [33].

3.3.3. Substance use

Patients with MDD commonly present with comorbid substance use; however, literature on the use of ECT for these patients is limited. Moss et al. found that mood related symptoms improved with ECT independent of comorbid substance (cocaine, heroin, or cannabis) and alcohol abuse; however, combined substance and alcohol abuse predicted poorer response [34]. Those with combined use experienced significantly less depressive symptom alleviation. A more recent study has shown that those with alcohol use disorder or other substance use disorder have lower remission rates (29% and 25.6%), than the patients who did not engage in substance use (46.8 and 41.8%, respectively) [35].

3.3.4. Summary of comorbid diagnosis findings

Overall data on comorbid diagnosis is limited. Available data indicates that borderline personality disorder and substance use disorders are negative predictors of ECT efficacy.

4. Laboratory/physiologic predictors and biomarkers

4.1. Genetic/epigenetic/proteomic

4.1.1. Genetic

Most available literature on genetic factors of ECT pertains to animal models. However, to maximize clinical relevancy this review will limit discussion to human data.

Glutamate Receptor Ionotropic Kainate 4 (GRIK4) gene is expressed in the hippocampus and modulates neuroplasticity [36]. Polymorphisms of this gene have been suggested to predict treatment response to ECT. In one study, patients with AA homozygotes at rs11218030 have better response to ECT as well as 5 times less relapse risk compared to those with G allele genotypes ($p = 0.000271$) [36]. GG rs1954787 ($p = 0.013$) and rs4936554 A allele ($p = 0.04$) genotypes were also risk factors for lack of response [36].

Catechol-O-methyltransferase (COMT), a dopamine metabolism enzyme, has been associated with ECT treatment response. Multiple studies find the more active COMT 158 val/val genotype favors ECT response [37]. Dopamine D2 receptor (C957T rs6277) and dopamine D3 receptor (rs37322790 T and rs3773679 G) polymorphisms have also been associated with ECT response and remission [37].

Serotonin pathway genes have also been associated with treatment response. Tryptophan hydroxylase 1 218CC genotype as well as serotonin transporter gene long/short promoter polymorphism (5-HTTLPR ll) coupled with norepinephrine transporter (NET) 182TT were associated with decreased treatment response [37]. Other studies of 5-HTTLPR alone found no association [37]. A study of serotonin 2A receptor polymorphisms rs7997012 and rs6311 found no correlation with ECT response [37].

One study of brain-derived neurotrophic factor (BDNF), a growth factor for neuronal differentiation and survival, has shown the rs11030101 TT genotype to be predictive of ECT response compared to the AT genotype [37].

Apolipoprotein E (APOE), an important factor in Alzheimer's disease, has been studied in the setting of ECT response and cognitive changes post ECT. APOE-ε4 was associated with better ECT response in patients with late-onset depression without psychosis; however, the association between treatment response and APOE variants could not be replicated in two larger studies [38].

4.1.2. Epigenetics

Most epigenetic research to date is in animal models; however, a recent human study has shown lower methylation rate of BDNF promotor is associated with remission of depression after ECT [39]. This preliminary study involved 11 patients and assessed BDNF serum levels and promotor methylation at various time points throughout a course of ECT. Compared to those that had remission of depression, non-remitters had significantly higher methylation rates throughout the full course of ECT ($p = 0.002$).

4.1.3. Proteomic

Serum assays for Pigment epithelium-derived factor (PEDF), a serine protease inhibitor with antiangiogenic, neurotrophic and neuroprotective properties, is decreased in patients with depression and significantly increases following ECT ($p = 0.03$) [40]. While this study did not find significant correlation between PEDF and clinical outcomes (HAM-D), it does provide preliminary framework for a proteomic strategy for identifying ECT predictors.

4.2. Hypothalamic-pituitary-adrenal axis

Overactivation of the hypothalamic-pituitaryadrenal axis as evidenced by failure to suppress cortisol by dexamethasone suppression test has been implicated in depression, especially with melancholic or psychotic features [41]. In a small study of 18 patients, reduction in HAM-D score after ECT was correlated with baseline cortisol non-suppression ($p = 0.049$) [41]. Cortisol non-suppression post ECT also predicts relapse [42]. This data highlights the role of HPA axis dysregulation in MDD and indicates that HPA function tests are predictive of ECT efficacy.

4.3. Neuroimaging

Longitudinal structural neuroimaging studies have shown that ECT increases volume in the hippocampus, amygdala, caudate nucleus, and medial and superior temporal lobe; however predictive models of treatment efficacy have been hindered by lack of statistical power [43]. The formation of the Global ECT-MRI Research Collaboration provides a platform for data sharing across sites and may lead to more effective identification of predictors of ECT response by strengthening statistical power [43].

Response to ECT is associated with resting-state connectivity, larger pretreatment amygdala volume, and smaller inferior frontal gyrus volume based on univariate group statistics [44]. One study attempted to improve prediction precision to an individual level by using a support vector machine to process multivariate patterns of voxels on pre ECT MRI brain. All patients started with unilateral electrode placement but were converted to bilateral if response was insufficient. This machine learning algorithm was able to predict individual ECT response with a 78.3% accuracy, with higher subgenual cingulate gyrus volume contributing the most to response prediction [44]. A second study voxel-wise machine learning on pre-ECT structural MRI identified several gray matter areas of interest including the right hippocampus/parahippocampus, right orbitofrontal gyrus, right inferior temporal gyrus, left postcentral gyrus/precuneus, left supplementary motor area, and left lingual gyrus. This study included three independent data sets: two used RUL ECT unless bitemporal was indicated, and a third used bifrontal ECT. This algorithm was able to predict response with 86%, 89%, and 90% accuracy in each of the three data sets [45].

Another study similarly used machine learning to predict treatment response by analyzing resting state functional MRI (fMRI), which yielded two network-based classifications: the first network, centered

on the dorsomedial prefrontal cortex and including the dorsolateral prefrontal cortex, orbitofrontal cortex and posterior cingulate cortex, predicted remission with positive predictive value of 88% (84% sensitivity, 85% specificity). The second network, centered in the anterior cingulate cortex and including the dorsolateral prefrontal cortex, sensorimotor cortex, parahippocampal gyrus and midbrain, had a positive predictive value of 80% (80% sensitivity, 75% specificity). RUL ECT was used for 82% of patients, BL ECT in the rest [46].

A second study using pre ECT fMRI machine learning algorithm focusing on basal brain activity and connectivity found that fronto-temporal connectivity is predictive of response, particularly between: 1) left fronto-parietal network and the supplementary motor network and 2) a superior temporal network and left lateral occipital cortex. Patients in this study received RUL ECT by default and were switched to bitemporal if clinically indicated. Models in this study were able to predict response with a balanced accuracy of 58–68% [47].

One study used random forest models incorporating pre-ECT and post-ECT MRI to predict relapse in the first 6 months following ECT course. Most patients received RUL while some BL was included. This study was able to predict relapse with a balanced accuracy of 71–78%. The cingulate isthmus asymmetry, pallidal asymmetry, paracentral to precentral cortical thickness ratio, and lateral occipital to pericalcarine cortical thickness ratio contributed most to the prediction of relapse [48].

4.4. Electroencephalogram

Electroencephalographic (EEG) data is widely available via the 2 channel EEG built into modern ECT devices. The prognostic value of computer analysis of digitized EEG data may be more promising than visual interpretation. In Pre-ECT EEGs, high baseline theta activity in anterior cingulate cortex and greater frontal interhemispheric coherence is associated with positive treatment response. Smaller fractal dimension (a statistical index of EEG complexity) after the first ECT session predicts response at 2 weeks of treatment. Intra-ictal EEG characteristics such as quality, frequency, and amplitude have not shown conclusive correlation with treatment response. During ECT sessions the magnitude of the induction of slow wave activity in the prefrontal cortex was correlated with response, while greater ictal power, delta coherence, and postictal suppression predict treatment response [49]. Greater pre-ECT anterior delta coherence is associated with treatment response ($p = 0.01$ and $n = 30$, $p = 0.008$ and $n = 40$ in separate trials) [50].

4.5. Polysomnography

Though the influence of specific sleep disorders, such as obstructive sleep apnea, on ECT effectiveness is beyond the scope of this review, polysomnography may provide useful prognostic value.

In a prospective study of 15 inpatients, higher baseline REM density of the first REM sleep period predicted better ECT remission ($p < 0.05$) [51]. This small study suggests further investigation is needed to evaluate REM density as a potential predictive candidate of ECT remission.

In one study patients were given polysomnography after ECT and reevaluated 6 months later for recurrence of depressive symptoms. Compared to those who remained well (GAS > 70), those who had reemergence of depressive symptoms had significantly shorter REM latency after completing a course of ECT. A REM latency of < 20 min confers a 67% risk of depressive symptoms by 6 months [52].

4.5.1. Summary of laboratory and physiologic predictors

A large body of literature is available in animal models; however, for maximum clinical relevance this review focuses on human models. Limited genetic data in human studies indicates predictive value of specific polymorphism of genes including GRIK4, COMT, dopamine D2 receptor, 5-HTTLPR 11/NET, serotonin 2A receptor, and BDNF. Multiple machine learning studies were able to predict ECT response based on pre ECT functional and structural MRI. EEG yields multiple predictive factors; however, computer analysis of digitized EEG is more useful than visual inspection.

5. Predictors of cognitive side effects post ECT

While ECT has been proven to be highly effective in treating depression, cognitive side effects are a concern for some patients. Research on the predictors of cognitive side effects post ECT is still limited. In this section we'll discuss baseline patient characteristics (age and pre-existing cognitive deficits) and disease states (Parkinson's) that might predict higher likelihood of memory and cognitive side effects of ECT. In short: baseline cognition does not appear to predict cognitive side effects, age predicts some difference in specific cognition tests but the difference disappears at timepoints longer than 3 days post ECT, and data on Parkinson's disease is inconclusive.

5.1. Effect of baseline cognitive deficits on cognitive side effects

In a prospective study of 54 depressed, elderly, patients, baseline cognitive tests were conducted on patients with no cognitive impairment (NCI) and patients with cognitive impairment but no dementia (CIND). This was done before treatment, 1 week and 3 months after ECT with patients randomized to RUL and bifrontal (BF) electrode placement. They found baseline cognitive tests did not predict cognitive side effects of ECT and that CIND patients were not more vulnerable to cognitive side effects than their NCI counterparts [53].

A prospective study of 44 elderly depressed inpatients split into NCI, MCI and dementia groups, measured MMSE at baseline, after the 6th ECT session, 6 weeks and 6 months post ECT. They found that overall, baseline cognitive deficits significantly predicted transient MMSE decline 6 weeks after ECT ($p = 0.007$) but was no longer significant at 6 months ($p = 0.55$). Of note, cognitive impairment improved significantly in NCI and MCI patients both 6 weeks and 6 months post ECT. Patients with dementia were more likely to show cognitive decline than the other two groups, but this result is difficult to generalize given that some patients underwent concurrent antidementia treatment while others did not [54]. Furthermore, given that cognitive decline is expected in the natural course of dementia, it is difficult to attribute the observed decline as a side effect of ECT without a comparator group.

5.2. Effect of age on cognitive side effects

A meta-analysis of 39 studies ($n = 1415$) explored age as a predictive factor of cognitive change following unilateral ECT. They found that higher age predicted larger decrease in executive function ($p = 0.00046$) when measured 3 days post ECT. They also found that higher age predicted smaller decrease in some memory abilities; verbal learning ($p = 0.0001$), semantic memory retrieval ($p = 0.047$) and visual recognition ($p < 0.0001$). After that, age did not predict change in cognitive performance [55].

5.3. Risk of cognitive side effects with Parkinson's disease

In a study of 11 patients with Parkinson's Disease who received ECT, cognition was assessed at baseline using WAIS-R, the Wechsler Memory Scale, the Auditory-Verbal Learning Test, and the Wisconsin Card Sorting Test. Baseline cognitive deficits were found in 3 of those patients. They found that Parkinson's patients maybe more vulnerable to cognitive adverse events post ECT as 7 patients developed post ECT delirium leading to discontinuation in most of these patients. Patients with baseline cognitive impairment maybe more vulnerable to cognitive side effects as 2 of these patients developed delirium [56].

A systematic review of 43 studies concluded that the evidence of

cognitive outcomes post ECT in depressed Parkinson's patients was inconclusive. Though they found no significant changes in cognition post ECT and some patients' cognition even improved, likely due to improvement of depression, there was a lack of consistent assessment of cognitive changes across most studies to allow conclusive findings [57].

6. Limitations

Limitation of this review includes that it was not a meta-analysis of the included studies. This review purposefully covered a wide range of the existing literature which required multiple heterogeneous studies that would not lend itself to pooling in statistical analysis. Lastly, this review is limited by the supporting literature, in that, not all the studies are as rigorous, with vastly heterogeneous participants and various techniques for ECT across studies. We reported the ECT technique used when available. However, many studies did not specify the technique used. Also, despite efforts to be as comprehensive as possible in this broad review, publication bias in the literature cannot be totally ruled out.

7. Conclusion

Regarding precision medicine, some fields have the luxury of sharper refinement than others, for example oncology uses specific tumor markers to guide selection of chemotherapy. Psychiatry does not have that type of precision. Instead, clinicians must synthesize a wide spectrum of (sometimes conflicting) factors when recommending ECT and prognosticating response at the level of the individual patient. This spectrum can be conceptualized roughly into demographic, clinical, and laboratory/physiologic factors.

Demographic data shows that older individuals benefit more from ECT, with the old-old (> 70 yrs) responding better than the young old. Race, gender, SEC do not appear to affect treatment efficacy. Review of the literature regarding issues of racial and socioeconomic factors revealed a paucity of data, highlighting a large disparity in the population of patients that receive ECT. Individualized medicine necessitates cultural competency and willingness to address these disparities.

Each clinical factor taken individually has subtle influence on the likelihood of ECT response but taken together can form a robust treatment plan tailored for an individual patient. Available literature supports the predictive value of several clinical factors. Suicidal ideation appears to predict response when utilizing BL electrode placement. Psychotic depression is a good predictor of response. Treatment resistance predicts poorer response. Depression severity, and melancholia show conflicting data. Limited data is available for catatonia specific to MDD, but overall data shows positive response of ECT for the treatment of MDD with catatonia. Limited data is available for comorbid psychiatric diagnosis commonly seen with MDD, including personality disorders and substance use disorders, indicated diminished efficacy. The efficacy of ECT vs other modalities of treatment for MDD with comorbidities was beyond the scope of this review but is another critical consideration.

Laboratory and physiologic based biomarkers provide exciting possibilities that may elevate the precision of ECT; however, lack of widespread availability (or some biomarkers) and lack of validation in larger studies limits current clinical utility. Genetic, epigenetic, and proteomic factors remain predominately in animal models but ongoing research in humans has identified several promising targets. Neuroimaging, augmented by machine learning, offers an exciting outlook for the future of precision psychiatry.

Declaration of Competing Interest

This work was supported by the office of Academic Affairs, Medical College of Georgia at Augusta University, Augusta, GA, United States (NY). Dr. Youssef discloses that he received research support in the last 3 years (but not salary support) from Merck & Co. and MECTA Corporation, the U.S. Department of Veterans Affairs, and August Biomedical Research Corporation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2019.07.001.

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