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**Title:** The role of clinical pharmacology and pharmacogenetics in electroconvulsive therapy: from safety to efficacy  
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Pharmacogenetics in Electroconvulsive Therapy and Adjunctive Medications

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ABSTRACT

Electroconvulsive therapy (ECT) has shown apparent efficacy in treatment of patients with depression and other mental illnesses who do not respond to psychotropic medications or need urgent control of their symptoms. Pharmacogenetics contributes to an individual’s sensitivity and response to a variety of drugs. Clinical insights into pharmacogenetics of ECT and adjunctive medications not only improves its safety and efficacy in the indicated patients, but can also lead to the identification of novel treatments in psychiatric disorders through understanding of potential molecular and biological mechanisms involved. In this review, we explore the indications of pharmacogenetics role in safety and efficacy of ECT and present the evidence for its role in patients with psychiatric disorders undergoing ECT.
INTRODUCTION

Due to its apparent effectiveness, electroconvulsive therapy (ECT) was commonly used for depressive disorders prior to invention of antidepressants in the 1950s. At the beginning, unmodified ECT was agonizing and unsafe, leading to, among others, bone fracture or spine injury. However, the advent of anesthetics and muscle relaxants along with newer apparatus evolved the “modified ECT to achieve maximum benefits while minimizing the procedural side effects related to the applied medication (anesthesia), electrical current or the induced seizure. ECT is currently administered with individually adjusted electrical currents under surveillance of anesthesiologists who apply anesthetics and muscle relaxants in appropriate medical setting. ¹

In spite of all the technical advances that have improved the relative risk of ECT, many crucial issues remain unresolved. For example, it is difficult to determine a priori whether ECT will be associated with an “adequate” therapeutically effective seizure in each patient. ² Genetic variations contribute to the variation of an individual’s response to different class of medications or treatment procedures via multiple components. This interface between our genetic variations and response to therapeutic interventions, i.e. pharmacogenetics, determines the individual response to a specific treatment and affects both patient’s safety and efficacy of response to ECT.

Historically, the role of pharmacogenetics in ECT was primarily related to the safety of ECT application and was explored by Kalow. Observation of prolonged apnea after succinylcholine administration in some individuals paved the way to the preliminary clinical insights into pharmacogenetics. In 1956, Kalow discovered that an alteration in plasma cholinesterase level caused induction of longer duration of paralysis by application of succinylcholine to ECT patients. This change resulted in extension of duration of succinylcholine action from the few minutes to over an hour in the affected individuals. ³, ⁴ Kalow implied the discovery of the presence of genetic effects on drug response. ⁵, ⁶

These studies advanced further research related to pharmacogenetics such that in 1960s the process of drug acetylation was discovered and the fact that slow acetylators (poor metabolizers) are more prone to side effects related to drug metabolism. ⁵ Furthermore, by application of anesthetics during procedural treatments including ECT, the awareness of developing side effects such as acute porphyric event due to thiopentone as well as the observed association of the malignant hyperthermia with succinylcholine, drew the attentions in the how genetics might influence in the applied pharmacology. ⁷
ECT is the most effective acute treatment for mood disorders, especially treatment-resistant Major Depressive Disorder (MDD), and has proven efficacy in other non-depressed psychiatric disorders such as schizophrenia. Several studies have explored the impact of genetics in the neurobiological mechanisms involved in ECT. These studies have also aimed to improve the efficacy of ECT by predicting the genotype-phenotype distinction of patients undergoing ECT. To our knowledge, no comprehensive literature review has been published on this ground. Hence, in this review, we will provide an evidence-based approach to the role of pharmacogenetics on safety (drugs used during ECT) and efficacy of ECT (potential genes and neurobiological mechanisms), and present evidence of its importance in patients with psychiatric disorders who undergo ECT (figure 1).

METHOD

Using a structured approach to identify the source of materials for the review, a systematic search was conducted for relevant peer-reviewed articles in PubMed and the Google Scholar search engine, using the keywords ‘ECT anesthesia genetics’, ‘ECT safety genetics’, ‘ECT efficacy genetics’, ‘ECT and genetics’, ‘treatment resistant psychotic disorders ECT genetics’, ‘depressive disorders ECT genetics’, ‘psychotic disorders ECT genetics’, ‘ECT neurotransmitter genes’, ‘genetics and ECT response’ and ‘adjunctive therapy in ECT and genetics’. References of the relevant articles or editorials were also considered for potential bibliographic related references to avoid any missing publication. All searches were limited to research published in English. Due to paucity of articles on this subject, there was no restriction on time of publication. The identified papers were predominantly related to depression disorders. For the efficacy of ECT and main focus of this review, we included all preclinical and human studies that might explain a direct role of a gene in the efficacy of ECT or suggest a genetic effect through neurobiological mechanisms. Accordingly, 34 publications were identified in investigating the pharmacogenetics in efficacy of ECT; only 19 articles showed direct investigation on role of pharmacogenetics in ECT. The ECT associated gene signatures were analyzed using MetaCore™ platform for investigation of their potential interactions and common biological network pathways in human brain.
PHARMACOGENETICS AND SAFETY OF ECT

I. Anesthesia adverse events

Abnormalities in butyrylcholinesterase

ECT is a short procedure and demands anesthetics with rapid onset and short duration of action. These qualities have made succinylcholine as the neuromuscular blocking agent (N MBA) of choice for ECT. The enzyme butyrylcholinesterase (BCHE) hydrolyzes ester bonds in succinylcholine. The enzyme is composed of 4 identical subunits of 574 amino acids, each containing an active catalytic site. The BCHE1 gene is located on four exons of chromosome 3q26.1–3q26.2 (online Mendelian inheritance in Man; OMIM 177400). The gene encodes a 602 amino acid protein including a 28 amino acid leader peptide. Genetic variation in the BCHE1 gene leads to variant enzyme forms, which affect the substrate behavior, resulting in reduced or absence of the enzyme BCHE activity. BCHE deficiency results in a prolonged effect of the ultra-short acting depolarizing muscle relaxant succinylcholine due to markedly decrease in plasma cholinesterase activity. The variants of BCHE included wild type (U), atypical (A, dibucaine resistant), fluoride resistant (F), silent (S) and Kalow (K). Besides the normal variant (U), A and K variants are more frequent (A20G and G1615A). It is noted that the patients with homozygosis or carriers with compound heterozygosity remain asymptomatic in the absence of exposure exogenous choline ester-compound such as succinylcholine.

In Australian population, out of 65 patients referred for prolonged post-succinlycholine apnea, 85% of the subjects showed one of mutated variants of BCHE gene including dibucaine (Dib; D70G), Sil-1 (G115FS), Flu-1 (T243M), Flu-2 (G390V), and K-variant (A539T), with 74% being dibucaine homozygote or heterozygote, 6% rare genotypes, 3% heterozygous fluoride allele, and 13% undetermined. The Danish Cholinesterase Research Unit (DCRU), in a 20-year longitudinal study, found abnormal response to succinylcholine in 61.1% of the 1,247 patients who were visited in the center. Of these 1,247 patients, 28.5% had normal genotype and 46.5% were genotypically aberrant. While the recovery time of neuromuscular function in patients with one aberrant allele was 15-30 min following a single dose of succinylcholine 1.0-1.5 mg kg⁻¹, it took 35-45 min for patients with heterozygosity of abnormal allele in two genes to recover. Homozygosity in abnormal allele in atypical gene lengthened the recovery time to 90-180 min. Patients with genotypes of AK and AH experienced slightly (20 min) or markedly longer duration of action (90 min) of succinylcholine, respectively. Accordingly, there are several case reports of succinylcholine induced prolonged apnea in patients receiving ECT. In a longitudinal study, Mollerup et al. determined the BCHE activity and the BCHE genotype of 13 patients who were visited in the DCRU after ECT. The authors measured and compared the duration of apnea with normal subjects and found BCHE gene
mutations, the K-variant being the most frequent. The duration of succinylcholine action and consequently duration of apnea were prolonged (5-15 min) in 11 patients compared with controls (3-5.3 min). Consequently, they recommended neuromuscular monitoring during the first ECT.

**Malignant hyperthermia**

Malignant hyperthermia (MH) is a hypermetabolic response to succinylcholine and potent volatile anesthetic gases such as halothane, isoflurane, sevoflurane and desflurane. Succinylcholine, the main applied muscle relaxant in ECT, is a far more powerful trigger of MH than the volatile agents. 22-24 Experimental studies indicate that the mechanism underlying MH is an uncontrolled release of intracellular calcium from skeletal muscle sarcoplasmic reticulum (SR). MH is inherited primarily in an autosomal dominant fashion in humans, which might result in the MH prevalence of up to 1: 3000 due to the causal genetic mutation. A more complex inheritance pattern might also be observed in the affected individuals. 25

Approximately 50% of MH related genetic variants have been found in the *RYR1* gene on chromosome 19, a calcium channel located in the sarcoplasmic reticulum. Most cases (70%) carry one of 30 *RYR1* mutations. Linkage studies have implicated five other regions, with variants identified in calcium channels *CACNA2D1* and *CACNA1S*. While these regions account for genetic variants in less than 2% of cases, the causal genetic variant in approximately 30% of patients remains unknown. 26, 27 Genetic tests may offer a non-invasive diagnostic method with lower morbidity than in vitro muscle contracture tests as the current functional gold standard for MH diagnosis; however, genetic testing is unreliable because the spectrum of contributing loci and alleles is not yet fully understood.

The reported incidence of MH during ECT has been less than other procedures requiring general anesthesia. It seems more likely that other factors may be responsible for this observation. Gornert indicated that MH is triggered in proportion to the total dose of triggering agents. 28 Thus, even if MH is triggered by succinylcholine during ECT, the absence of continued administration of succinylcholine may abort its more fulminant expression. Indeed, the anesthetics used in ECT are almost always ultra-short or short acting barbiturates such as methohexital or propofol. Absence of the use of volatile anesthetics in ECT also may explain the lack of induction of MH. As was previously stated potent volatile anesthetics that are commonly employed in general anesthesia are also strongly linked to precipitation of MH. 29
Neuroleptic malignant syndrome

NMS is a serious and potentially fatal side effect of antipsychotics, consisting of fever, muscle rigidity, delirium and autonomic dysfunction. Underlying mechanism of this side effect is still unknown and debated. So far some risk factors have been identified, with clinical observations and recent pharmacogenetic research suggesting, though with inconsistent findings, correlation between genetic mechanisms and predisposition to NMS. Polymorphisms of CYP2D6 enzyme through which most psychotropic drugs are metabolized and TaqIA DRD2, a target for antipsychotic drugs, has been reported to act as the link between pharmacogenetic factors and the potential development of NMS. In spite of these genetic links, ECT has been reported to be useful for refractory NMS or improving NMS symptoms. Further investigation in an appropriately designed study is warranted to investigate the treatment role of ECT in NMS and identify the subset of patients with NMS who might benefit from this procedure.

II. Potential neurobiological mechanisms in cognitive side effects of ECT

There are some animal and human preliminary evidences on the role of neurotransmitters/biological alterations with the adverse cognitive effect of ECT. The investigated systematic alterations include cholinergic, endogenous opioid, glucocorticoid and glutaminergic systems, which were mostly conducted in animal models. Among these, the effects of glutaminergic and glucocorticoid compounds have been investigated in human studies. In an ECT trial of 10 subjects, using ketamine as anesthetics resulted in less impairment of short-term memory than applying etomidate. The result is suggestive that the ECT-induced cognitive disruption might be mediated by glutamate at N-methyl-d-aspartate receptors. Neylan et al., in a two-week ECT-trial of 16 subjects, showed that elevated basal level cortisol was associated with greater degree of ECT-induced cognitive impairment.

Palmio et al., in two separate studies, investigated the acute effect of ECT on the perturbations in the amino acid transmitters and the brain biomarkers in blood with potential role in neuronal activity and neuronal injury. In TRD-MDD patients who underwent a single ECT session, they showed significant changes in the serum levels of glutamate, aspartate, gamma-aminobutyric acid (GABA), S-100b protein (S-100b), tryptophan, and some other amino acids in 24 hours. However, it is important that future studies are designed to better distinguish changes in the levels of these biomarkers related to both ECT side effects on brain and therapeutic response.
Pharmacogenetics and the efficacy of ECT

The effect of adjunctive psychotropic drugs on ECT outcome

The current remission rates after ECT appear to have declined. In a meta-analysis to investigate the effect of previous pharmacotherapy failure on the efficacy of ECT, the overall remission rate was reported to be 48.0% (281 of 585) and 64.9% (242 of 373) for patients with and without previous pharmacotherapy failure, respectively. Additionally, patients who received previous pharmacotherapy but failed to respond to the treatment, showed reduced efficacy of ECT. ECT has shown higher efficacy in conjunction with antidepressants and antipsychotics. Accordingly, the understanding of pharmacogenetics of the adjunctive drug therapy and more comprehensively pharmacogenomics of such treatments has the potential to improve therapeutic outcomes of ECT and individualized drug therapy, while avoiding toxic effects and treatment failure. Genetic predictors of antipsychotics have been widely studied, but fewer evidences are available how these factors might influence their role in the outcome ECT.

Some studies provide evidence that the application of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (0.5 mg/kg) could provide rapid and longer antidepressant effects after ECT. These studies have suggested the involvement of synaptic plasticity and neurotrophic signaling in the mechanism of action of ketamine. The observation of mammalian target of rapamycin (mTOR) and Brain-Derived Neurotrophic Factor (BDNF) pathway activation by NMDA receptor antagonism has proposed the observed link for the antidepressant action of ketamine through the interaction between plasticity-related signal pathway.

Using ketamine (0.5 mg/kg) been promising in depressive patients prior to ECT. Some evidences that ketamine might reduce the effect of ECT on memory has drawn more attentions to application of ketamine for ECT. The optimal adjunctive dose range of ketamine, its safety and effective duration of action should be further investigated.

The association between carrier status for the long allele of serotonin transporter gene with a better response to serotonin selective reuptake inhibitors (SSRIs) has been of interest. Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4) encodes the serotonin transporter and is located on location 17q11.1–q12. Rasmussen et al. retrospectively studied whether the polymorphism of the serotonin transporter gene (5-HTT) was associated with differential treatment response in 83 ECT patients treated for depressive disorder. No significant association was found between serotonin transporter gene allelic status with several characteristics of ECT treatment, such as seizure length or threshold, number of treatments in a series, and depression scale ratings.
Potential pharmacogenomics (neurobiological mechanisms) in the efficacy of ECT

I. Brain Alterations in Acute and chronic ECT response

As was previously stated, for many non-responsive patients to psychotropic drugs, ECT is an efficient rapid intervention. However, the neurobiological mechanisms for the efficacy of ECT remain unknown.

While some of the therapeutic response to ECT is shortly observed after treatment, similar to psychotropic drugs, efficacy of ECT increases by repeating treatment. This fact has made neurotransmitters and metabolic enzymes of greater interest for investigation of ECT response. ECT affects wide range of brain areas, which the potential therapeutic effects on these regions may be through structural, and/or biochemical changes.

Several neurotransmitters have been investigated involvement in association with psychotic disorders. Yatham et al. suggested the role of serotonin (5-hydroxytryptamine, 5-HT) dysfunction. Using positron emission tomography (PET) study in patients with bipolar disorders, they showed antidepressants down regulate 5-HT receptors in several cortical regions. In a follow-up study in patients who treated with ECT due to refractory response to antidepressants, they showed similar effect by ECT in down-regulation of brain 5-HT receptors in the limbic and prefrontal cortical brain areas. Similarly in another study by Lanzenberger et al., PET scan showed substantial reduction of 5-HT1A receptor-binding potential (BPND) almost across the entire cortex after one ECT, particularly in amygdala and anterior cingulate cortex. However in another study, after several ECT, BPND did not show consistent result with the former study.

Dopamine neurotransmitter has also been of interest in understanding the refractoriness of response to treatment in depressive disorder. Saijo et al. scanned seven MDD patients’ brain after 6-7 ECTs using PET to examine the effect treatment on Dopamine D receptors. They found significant increase in D receptors of anterior cingulate of patients who received ECT. Although these studies shows regulatory role of serotonergic and dopaminergic pathways in biological mechanisms involved in response to ECT, it is yet to be discovered how ECT cause this alterations.

A few studies on depressive disorders have explored the hypothesis of altered connectivity within the white matter (WM) microstructures between the frontal and limbic areas, such that WM abnormalities relate to depression severity and TRD. Accordingly, Lyden et al. demonstrated ECT effect on structural plasticity within dorsal fronto-limbic pathways and plasticity of WM relation to therapeutic response in depression. It is unknown if there is any genetic predisposition to these structural alteration, and future investigation is hence
warranted.

II. Potential genes involved in ECT response and the related biological pathways

In 1998, Fochtmann et al. showed that both hippocampal A1-receptor, and cortical and striatal NMDA-receptor bindings are associated with the quality of seizure (i.e., duration). Their study suggested that induced ECT-neurobiological mechanisms potentially related to some genes, might contribute to the desired therapeutic effect of ECT.

While genetic pathway alterations by ECT and their association with clinical parameters could provide pivotal information, few studies have examined the genetic approaches to neurobiology of ECT and the impact of pharmacogenomics on treatment response in ECT (Table 1). These studies have shown that chronic molecular effects induced by ECT are more likely to reveal the mechanisms of its therapeutic effects.

A. Gene expression signatures

Studies have suggested that the therapeutic effects of ECT might be due to mechanisms involving several amino acid transmitter changes in brain through overexpression of their regulatory genes. Altar et al. investigated the effects of single versus repeated electroconvulsive seizure (ECS) exposure on gene transcription, in an animal model, to identify genes and potential biochemical pathways that are associated with the efficacy of chronic ECT. Almost one hundred and twenty hippocampal and frontal genes were differentially expressed within distinct pathways (particularly BDNF-MAP kinase) in response to acute and chronic ECS. Of those, only nineteen genes showed similar expression in response to acute or chronic ECS. Brain-Derived Neurotrophic Factor (BDNF), cyclooxygenase (COX)-2, neuronal activity-regulated pentraxin (Narp), and TGFβ-inducible early growth response had co-directional changes in both brain regions. They suggested that the genes that increase only with chronic ECS are more likely to be associated with efficacy of ECT, including those of the BDNF-TRKB-MAP kinase pathway, arachidonic acid pathway, vascular endothelial growth factor (VEGF), thyrotropin-releasing hormone (TRH), neuropeptide Y (NPY), and regulators of neurogenesis.

To address the therapeutic efficacy of ECS, Newton and colleagues examined the expression of neurophins and related signaling pathways in the hippocampus of rats in response to ECS using a custom growth factor microarray chip. They reported the regulation of several genes that are involved in growth factor and angiogenic-endothelial signaling, including neuritin, stem cell factor, VEGF, (VGF), COX-2, and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). Some of these, as well as other identified growth factors, including VEGF, fibroblast growth factor, and BDNF, have effects on brain neurogenesis and cell proliferation. They also examined gene expression in the choroid plexus and found several enriched growth factors
in this vascular tissue, which were affected by ECS. Among the identified genes, TIMP-1 and COX-2 were highly expressed in both acute and chronic ECS. The authors suggested that the simultaneous augmented growth factor signaling with angiogenic process could have an important role in the mechanism underlying the therapeutic effect of ECT.

**B. Single gene approach: expression or polymorphism based**

In this approach a prior knowledge or presuppositions on a gene which directly or in directly may play a role in neurobiological mechanisms involved in efficacy of ECT response was used for investigation.

**DARPP-32**

DARPP-32 protein (dopamine- and cyclic-AMP-regulated phosphoprotein of molecular weight 32,000) has been of interest due to its phosphorylation regulation by dopamine and cAMP in nerve, which might mediate some dopamine effects. DARPP-32 gene down-regulation has also been implicated in schizopherenic patients. Accordingly, Rosa et al. showed that DARPP-32 expressions in striatum and hippocampus of rats increased after five ECSs in 48 hours. However, the effect was fluctuant and transient.

**COMT and APOE**

Catechol-O-methyltransferase (COMT), a major enzyme in dopamine metabolism in the prefrontal cortex has been of interest in response to efficacy of ECT. Anttila et al. showed that COMT high-high genotype carriers would be more common in responders to ECT than other genotype carriers. A finding that suggested the lower dopamine levels in the prefrontal cortex could be associated with substantially better treatment effects of ECT.

COMT Val158Met, a functional polymorphism of COMT at codon 158 substantially affected the dopaminergic activity such that the Met allele homozygosity resulted in considerable reduction of enzymatic activity compared with the Val allele homozygosity.

Domschke et al., in further investigation on val158met COMT, proposed that the impact of the SNP on the efficacy of ECT in depressive patients could be gender-specific. They also suggested that the val158met carrier might be less pharmacologically responsive to antidepressant and could benefit from ECT in their earlier stage of mood disorder.

**DRD2 and mutual effect with COMT**

Huuhka et al. investigated the synergistic effect of two polymorphisms of Dopamine 2 receptor gene (DRD2) and COMT, C957T (rs6277) and Val158Met (rs4680) in response to ECT treatment. The study groups consisted of 118 depressive patients and 383 healthy controls. They showed that had MT Met allele and DRD2 T allele had synergistic effect in prediction of severity of depression. Furthermore, they found that the patients with TT
Table 1. The pharmacogenetic studies related to the outcome of ECT in animal and human subjects.

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<td>Fochtmann et al.</td>
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### Pharmacogenetics in ECT and Adjunctive Medications

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<td>Huuhka et al.</td>
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<td>Anttila et al.</td>
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<td>Gedge et al.</td>
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<td>ECT did not increase serum levels of BDNF or rTMS</td>
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<td>Dannowski et al.</td>
<td>The International Journal of Neuropsychopharmacology/2013</td>
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<td>Change in MADRS, testing the association of two BDNF polymorphisms, rs11030101 and rs61888800</td>
<td>rs11030101 is associated with the efficacy of ECT.</td>
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genotype of DRD2 C957T SNP and Met/Met genotype of COMT were less likely to reach remission than those with CC genotype of DRD2 C957T and Val/Val genotype of COMT. Accordingly, they suggested the combined effect of these polymorphisms might be associated with response to ECT. 13

APOE and RGS4
Huuhka et al. also examined the apolipoprotein E (APOE) well known for its association with neurodegenerative diseases as well as RGS4 in prediction of TRD-MDD and found no association between APOE and RGS4 polymorphism and response to ECT. 69, 71 This finding was, however, not consistent with the only previous study on the association of APOE and ECT responders. 68

DRD3 (DR3)
To follow up on the role of dopamine D receptor gene in efficacy of ECT and evaluate the potential impact of dopamine D receptor gene (DRD3) variation on ECT outcome in treatment-resistant major depression, Dannlowski and colleagues used 10 genetic markers with high coverage percentage on DRD3 to investigate the association with response to ECT in 104 treatment-resistant MDD white patients. They found significant association of rs3732790, rs3773679 variants of DRD3 with response to ECT (p=0.02 and 0.03, respectively) and rs9817063 SNP with remission (p=0.01) after ECT. They suggested that DRD3 gene variation might affect the efficacy of ECT that might potentially be mediated through neurobiological pathways of striatal activity. 80
BDNF

BDNF is a member of the nerve growth factor family of neurotrophins. BDNF has been shown to exert important functions in neuronal survival, proliferation, and synaptic plasticity in the brain. There are several biological evidences to support the role of BDNF as a central neurotrophic factor in the efficacy of ECT. These evidences have shown the inductive effects of both single and repeated ECT on BDNF secretion in brain that are reflective of BDNF changes in serum. Similarly, BDNF levels are shown to decrease in individuals with depression and increase following antidepressants; the changes that correlates with the severity of the disorder. Accordingly, it has been suggested that BDNF may at least in part explain both the acute and chronic potent effects of ECT in depressive disorders.

The neurobiological mechanisms of action in ECT have been proposed to be involvement in, the induction of BDNF secretion by prolonged increase of both BDNF and TRKB (NTRK2) mRNA expression in the hippocampus and entorhinal cortex (EC). However, Taliaz et al. suggested that while neuroplastic alterations, as expressed by changes in BDNF expression within different brain regions, might be induced by ECT, the antidepressant-like effect of ECT in an animal model depends on reduction of the ventral tegmental area (VTA) BDNF expression but not on the elevation of hippocampal BDNF expression.

In an animal experiment, Segawa and colleagues tried to explain the role BDNF and pro-BDNF in acute and chronic ECT treatment. They found that single administration of ECS rapidly increased hippocampal levels of pro-BDNF along with levels of prohormone convertase 1 (PC1) and tissue-plasminogen activator (t-PA). These two proteases are involved in intra- and extracellular pro-BDNF processing. Further ECSs resulted increase hippocampal level of pro-BDNF as well as mature BDNF level. Taken together, they suggested that while PC1 and t-PA could both be involved in pro-BDNF processing connected with acute antidepressant effect of ECT, t-PA might play a dominant role following repeated ECS. In their model, chronic administration of imipramine significantly increased mature BDNF levels, but not pro-BDNF and protease levels, indicating that the therapeutic mechanism of antidepressants might differ from that of ECT.

Clinical studies support some of the obtained evidences by pre-clinical studies on BDNF. The significant increase in serum levels of BDNF has been detected in patients undergoing chronic ECTs. A possible mechanism for this observation has been proposed to be due to BDNF gene upregulation mediated by histone H3 and H4 acetylation, though in pre-clinical setting. Viikki and colleagues, in a recent study of 119 depressive patients, investigated the association between BDNF polymorphism rs11030101 and the efficacy of ECT. Their study demonstrated that the TA genotype carriers of rs11030101 were less likely to show
improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) and benefit from ECT compared with patients with the TT genotype. 91

VEGF, P2RX7 and HTR2A
Viikki et al. also examined the association between the VEGF 2578 C/A polymorphism and ECT in of 119 patients with TRD who were treated with ECT and 98 depressive patients treated with SSRIs compared to healthy controls. According to their findings, the CC genotype of VEGF 2578C/A polymorphism was more common in patients treated with ECT and SSRI than in healthy controls (31.1%, 25.5% and 18.7% respectively; p=0.056). The VEGF 2578 C/A polymorphism was associated with treatment resistant depression and CC genotype was more frequent in patients underwent ECT than in controls (31.1% and 18.7% respectively; p=0.015). 92 In the same study groups, they investigated the rs2230912 and rs2230912 P2RX7 polymorphisms. Neither of these two P2RX7 SNP was associated with either remission after SSRI or ECT. 93 In the same study populations, they investigated the improvement of depression using MADRS score after ECT in association with rs7997012 and rs6311 HTR2A polymorphisms. None of the SNPs were associated with the change in MADRS score due to treatment. However, the interaction between the SNPs and gender explained 14% of the variance in MADRS score change. 94

CREB
Fizzled 6 (FZ6) is a seven transmembrane-spanning receptor involved in Wnt signaling. This signaling pathway is one of the essential mechanisms in cell proliferation, polarity and fate determination during embryonic development and tissue homeostasis. 95, 96 The main signaling pathway is activated by FZ/β-catenin, FZ/Ca2+ and FZ/planar cell polarity signaling pathways 97 and inhibited by Dickkopf (Dkk) family members (e.g. Dkk1 which functions as secreted Wnt antagonists by inhibiting Wnt coreceptors LRP5/6). 98 Voleti et al. demonstrated that chronic administration of ECS augments the activity of several hippocampal genes through the cAMP-response element binding (CREB) such that subsequent effects might lead to the effectiveness of chronic ECT. FZ6 was also one of CREB-target genes, which was affected by chronic ECS. In their study, viral vector-mediated inhibition of Fzd6 produced anxiety and depressive-like effects. 99 Accordingly, the authors suggested that the activation of CREB might have regulatory effect on multiple functional pathways such that the therapeutic effect of ECS is dependent on a particular set of CREB-activated genes. 99

ACE
The angiotensin I-converting enzyme gene (ACE) has been suggested as a major gene affecting affective disorders and their treatment. To compare the effects of the ACE genotype distributions and treatment response to ECT in MDD patients, Stewart et al. studied 119
treatment-resistant depressive patients who were referred for ECT. All participants were genotyped for ACE, and the efficacy of ECT was evaluated using the MADRS. ACE genotype was not associated ECT efficacy and did not show a different frequency with healthy controls.

Discussion and future perspective

Our review demonstrates that the knowledge for safe application of ECT treatment of major depression and other psychiatric disorders has been improved, at least partly due to the role of pharmacogenetics in application of anesthetic agents. Some genes such as CACNA2D1 and CACNA1S, BCHE and RYR1 are associated with safe practice of anesthesia in ECT. While our review demonstrates that at this point, the knowledge of the mechanisms underlying the efficacy of ECT has not been thoroughly elucidated, we identified several genes (i.e. BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB and NMDA receptor), which their transcriptions might play important role in treatment response to ECT. It is important to identify the neural and the molecular pathways related to these that might explain the mediation of the behavioral changes by ECT and its timely application.

An ideal shock treatment produces two sets of acute and chronic neurobiological responses that result in a rapid and sustained treatment response for treatment of psychological disorders. Accordingly, Altar et al.’s experiment showed that the neurobiological mechanisms during ECT substantially differ by chronicity. More importantly they showed that a subset of genes would continue to be similarly expressed in some brain regions by both acute and chronic ECT. This fact could be suggestive that efficacy of ECT could be due to some common regulatory pathways modulated by the therapeutic stimulus. Investigating the potential brain regulatory network pathways among the abstracted genes (BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2 and TRKB), we identified that all genes or their transmitters are co-expressed as part of transcriptionally regulatory sub-networks in brain, more prominently in the frontal lobe (Figure 2 & 3). In these sub-regulatory networks, AP-1 transcription including CREB demonstrates the most regulatory effects on the network objects. This takes on greater significance that effectiveness of ECT is more dependent on treatment response to its chronic application. Consistently, Hope et al. showed AP-1 complex had high expression by administration of chronic ECT and persisted to be highly expressed by 7 days after the last ECT. It has been shown that AP-1 modulation affects many cell processes including cell proliferation, differentiation, transformation, neuronal activity and growth factor signaling. More importantly, it has been suggested that AP-1 could act as an environmental biosensor in mediating the linked cellular biological process.

There are other factors that might affect the variations in expression levels in brain regions
Figure 2. The demonstration of regulatory pathways among BDNF, COMT, DDR2, DDR3, CREB TRKB, and NMDA receptor in human brain. AP-1 complex shows the most regulatory effect on the genes of interest. Green arrows demonstrate activation and red arrows deactivation.

Figure 3. The demonstration of regulatory pathways among AP-1 complex, Cox2, and VEGF in human brain.
and directionality of regional regulatory networks. For example, there is evidence of variations in activity level of BDNF transcripts in different brain regions \textsuperscript{88, 104} or other patients’ clinical characteristics such as gender might influence some observed gene polymorphisms in response to treatment. \textsuperscript{94}

In spite of all the improved knowledge on the safety of ECT and its proved efficacy in treatment of some psychiatric patients unresponsive to medical therapy, ECT is still a physical intervention and more cumbersome than medications with higher efficacy. Accordingly, our understanding the acute and chronic molecular, cellular, and behavioral changes by ECT will provide a new view to find potential targets for novel psychotropic treatments, particularly antidepressants, that are highlighted by the findings such as regional gene induction (e.g. BNDF, Cox-2), increased neurogenesis, electrophysiological reactivity, the role of VEGF in neurogenesis, \textsuperscript{105, 106} and DARPP-32 expression. \textsuperscript{78} Some genes and associated pathways such as BDNF, TRKB-MAP kinase pathway, NPY, VEGF, arachidonic acid pathway, TRH, VEGF, and neurogenesis regulation pathways, which have shown differential expressions due to chronic stimulation by ECT, are more probable to have an intermediary role in benefiting from the long-term effects of ECT. These evidences along with shared regulatory pathways such as AP-1 and CREB could be useful for further investigation to identify novel gene targets for treating treatment resistant psychological disease.

Palfreyman et al. suggest illustrating a “disease signature” and “drug signature” of aberrantly expressed genes from comparison of normal controls and patients. \textsuperscript{107} In this approach, the genes associated with disease will be explored. The comparison of the spotted genes with ECT signature genes could identify a set of targets whose alteration might be a better predictor of disease and the effect of procedural treatment. Ultimately, such overlapping genes could be used to identify drug compounds that show similarity in inducing the gene expressions, which consequently mimic the therapeutic response of ECT. This method has been applied in animal mode such that \textsuperscript{108} several compounds have been investigated to identify the one that alter the same eleven genes elevated by ECT or exercise in rat brain. Of note, exercise has been favorably compared to antidepressant treatment for treatment of mild to moderate depression. \textsuperscript{108-110} Such compounds could also be used to augment the induced differentially genes expressions by chronic exposure to ECT or by antipsychotics. \textsuperscript{55} Further well-designed longitudinal clinical studies are required to increase our knowledge of the mechanisms underlying the efficacy of ECT.
Executive summary

Pharmacogenetics and safety of ECT

I. Anesthesia adverse events

Abnormalities in butyrylcholinesterase

- BCHE deficiency could result in a prolonged effect of the ultra-short acting depolarizing succinylcholine, the muscle relaxant of choice ECT, due to markedly decrease in plasma cholinesterase activity.

- Succinylcholine duration of action is prolonged for the patient with heterozygous for the K-variant allele, the most frequent variant.

Malignant hyperthermia

- Approximately 50% of MH related genetic variants have been found in the RYR1 gene on chromosome 19.

- Most cases (70%) harbor one of 30 RYR1 mutations.

- CACNA2D1 and CACNA1S variants account for less than 2% of cases and the causal genetic variant in approximately 30% of patients is unknown.

- The reported incidence of MH during ECT has been less than other procedures requiring general anesthesia.

Neuroleptic malignant syndrome

- CYP2D6 polymorphism, the enzyme through which most psychotropic drugs are metabolized and TaqIA DRD2, a target for antipsychotic drugs, has been suggested the link between pharmacogenetic factors and the potential development of NMS.

- In spite of these genetic links, reliable NMS during ECT has been reported.

II. Potential neurobiological mechanisms in cognitive side effects of ECT

- ECT-induced cognitive disruption might be mediated by glutamate at N-methyl-d-aspartate receptors.

  - Using Ketamine as anesthetics during ECT might result in less impairment of short-term memory

- Higher basal level of cortisol might be associated with greater degree of ECT-induced cognitive impairment.
• Acute effect of ECT causes perturbations of several amino acid transmitters and the brain biomarkers in blood with might be associated with neuronal activity or potential neuronal injury.

Pharmacogenetics and the efficacy of ECT

The effect of adjunctive psychotropic drugs on ECT outcome
• The current remission rates after ECT appear to have declined
  - The overall remission rate has been reported to be 48.0% and 64.9% patients with and without previous pharmacotherapy failure, respectively.
• ECT has shown higher efficacy in conjunction with antidepressants and antipsychotics
• Application of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine during ECT might augment rapid and longer antidepressant effect of ECT.
  - NMDA receptor antagonism could activate mammalian target of rapamycin (mTOR) and Brain-Derived Neurotrophic Factor (BDNF) pathways.

Potential pharmacogenomics/neurobiological mechanisms in the efficacy of ECT
I. Brain Alterations in Acute and chronic ECT response
• ECT affects wide range of brain areas.
• Therapeutic effects on brain regions may be through structural, and/or biochemical changes
• ECT could have similar effect like antidepressants in down-regulation of brain 5-HT₂ receptors in the limbic and prefrontal cortical brain areas.
• ECT could augment the increase in Dopamine D₂ receptors in some brain areas in patients who received ECT.
• ECT might effect on structural plasticity within dorsal fronto-limbic pathways and plasticity of WM relation to therapeutic response in depression

II. Potential genes involved in ECT response and the related biological pathways
A. Gene expression signatures
• Therapeutic effects of ECT might be due to mechanisms involving several amino acid transmitter changes in brain through overexpression of their regulatory genes.
• There are some similarities in ECT induced regional alterations, e.g. hippocampus and frontal lobe

• Several genes such as VEGF, VGF, COX-2 and TIMP-1 involved in growth factor and angiogenic-endothelial signaling could be co-expressed by both acute and chronic ECT.

B. Single gene approach: expression or polymorphism based

• Several individual genes have been investigated in association with ECT efficacy.

• ECT could transiently increase DARPP-32 expressions in striatum and hippocampus.

• The combined effect of COMT and DRD2 polymorphisms might be associated with response to ECT. COMT high-high genotype carriers would be more common in responders to ECT than other genotype carriers.

• DR3 rs3732790, rs3773679 SNPs are associated with remission after ECT.

• Both single and repeated ECTs increase BDNF secretions in mRNA expression, mostly in the hippocampus and entorhinal cortex.

  - The BDNF change in brain is reflective of changes in serum

  - PC1 and t-PA could both be involved in BDNF expression processing connected with acute antidepressant effect of ECT; t-PA might play a dominant role following repeated ECS

  - TA genotype carriers of rs11030101 was shown to be less likely to show improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) and benefit from ECT compared with patients with the TT genotype

• VEGF 2578 CC genotype was observed with more frequent in patients underwent ECT.

• CREB might have regulatory effect on multiple functional pathways such that the therapeutic effect of ECS is dependent on a particular set of CREB-activated genes.

Discussion and future perspective

• BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB and NMDA receptor are genes that their functions could affect the efficacy of ECT.
• The potential genes involved in efficacy of the ECT or their transmitters are co-expressed as part of transcriptionally regulatory sub-networks.

• In these sub-regulatory networks, AP-1 transcription including CREB could be a major regulator of the network objects.

• AP-1 complex has shown high expression by administration of chronic ECT and persists to be highly expressed by 7 days after the last ECT.

• The shared regulatory pathways such as AP-1 and CREB could be useful for further investigation to identify novel gene targets for treating treatment resistant psychological disease.

• Investigating ECT signature genes as compared to different drug compounds could help in identifying medications that might augment the induced differentially gene expression by ECT.

• Further well-designed longitudinal clinical studies are required to increase our knowledge of the mechanisms underlying the efficacy of ECT.
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