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Review article

DNA methylation and clinical response to antidepressant medication in major depressive disorder: A review and recommendations

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HIGHLIGHTS

- Research into the role that epigenetic mechanisms play in Major Depressive Disorder has grown rapidly over the last decade.
- Studies examining epigenetic mechanisms in psychiatric treatment response are rapidly emerging.
- We examine articles investigating DNA methylation and clinical antidepressant response in Major Depressive Disorder.
- Conclusions include a summary of current limitations and suggestions for future directions.

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ABSTRACT

Antidepressant medications are the most common treatment for major depression and related disorders. Pharmacogenetic studies have demonstrated that response to these medications is associated with genetic variation. While these studies have been invaluable they have yet to explain why a significant number of patients do not respond to their initial medication. The epigenetic modification known as DNA methylation has recently been studied in the context of antidepressant treatment response. As such, the purpose of this article is to review the advances made in the relatively new field of pharmaco-epigenetics of antidepressant response. We included all published articles examining DNA methylation in association with antidepressant treatment response in Major Depressive Disorder from April 2006 to June 2016 using the PubMed, Medline, PsychInfo and Web of Science databases. At the present time, although original articles are limited, epigenetic modifications of *SLC6A4*, *BDNF*, and *IL11* genes are showing promising results as biomarkers for prediction of antidepressant response. However, research methods and results are heterogeneous and additional studies are required before results are generalizable. At the end of this review we provide recommendations for study design and analytic approaches.

Contents

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1. Introduction

1.1. Major depressive disorder

This review is limited to data from studies of clinical response to antidepressant medications in Major Depressive Disorder (MDD); however, many aspects of antidepressant response can be applied to their use in anxiety and milder forms of depression and are directly applicable to personalized medicine in psychiatry. MDD is a highly prevalent, disabling, and costly healthcare issue, with evidence for a strong and complex genetic component [1,2]. The DSM-5 classifies MDD as a mood disorder with symptoms that must be present for two months or longer and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning [3]. DSM-5 lists the following as possible symptoms: pervasive sadness, loss of ability to experience pleasure, fatigue, weight changes, sleep disruption, cognitive impairment, and suicidal ideation. Approximately 12 per 100,000 lives are lost to suicide annually in the United States [4]. In addition to this mortality, MDD patients are at increased risk of developing other medical conditions, including coronary artery disease and type 2 diabetes [5,6]. Furthermore, MDD can affect the course of many other medical conditions [7]. According to the World Health Organization [8], MDD is actually the leading cause of disability world-wide, when considering total years lost due to disability, contributing substantially to the global burden of disease. The neurobiological foundations of MDD have been extensively studied using a variety of methodological approaches from the molecular level to behavioural animal models to imaging and electrophysiological techniques. Yet, the exact etiology of MDD remains unknown. However, research suggests some cases of MDD may result from mechanisms that include a maladaptive, neuroplastic response to stress in specific areas of the brain [9]. In recent years, the Research Domain Criteria (RDoC) system has been developed to integrate the many areas of neuroscience research with psychopathology and transition from DSM usage to a multidimensional approach [10,11]. In this context, it is notable that antidepressant medication is not constrained to specific DSM-5 nosology, but rather, is prescribed across many symptoms and numerous disorders.

1.2. Genetics of MDD

Many psychiatric disorders can be described as being highly heritable; however, MDD is an exception displaying the lowest heritability estimate of all psychiatric disorders at 0.37 [12]. MDD, like most psychiatric disorders, involves complex inheritance – while a clear genetic component is observed, the pattern does not fit traditional Mendelian models of disease. Epidemiologic studies of MDD date back to the the 1920s [13]. More recently, modern molecular genetic approaches have been used in an attempt to identify specific risk variants and have uncovered the involvement of multiple genes in disease predisposition (see Smoller [13] for an in-depth review of genetic findings in MDD and other stress-related disorders). Two genetically driven hypotheses have dominated MDD research – the monoamine hypothesis and the neuroplasticity hypothesis. Specifically, genes involved in several pathways have been implicated in depression including serotonergic, glutamatergic, monoaminergic, neurotrophic and hypothalamic-pituitary-adrenal (HPA) axis related genes. Genes in these same pathways have also been implicated in antidepressant response. For example, brain-derived neurotrophic factor (BDNF) is a protein involved in the neurotrophin growth factor system and genetic variation of the *BDNF* gene has been associated with MDD, suicide attempts, vulnerability to stressful life events, and antidepressant efficacy [14]. BDNF is known to play an important role in hippocampal neurogenesis and its isoforms are modulated by serotonergic agents, making it an obvious target for antidepressant treatment [15,16]. Furthermore, genetic polymorphisms located in the FK506 binding protein 5 (*FKBP5*) gene have also been associated with increased number of depressive episodes, rapid response to antidepressant treatment, and stress hormone dysregulation [17–19]. The *FKBP5* gene encodes for the FK506 binding protein 51, a member of the immunophilin protein family. The FKBP51 protein has been shown to be part of the HPA axis as it functionally interacts with the glucocorticoid receptor (GR), acting as a co-chaperone which regulates GR sensitivity [20]. However, candidate gene studies have not been well-replicated and even large-scale genome-wide association studies (GWAS) have yet to fully decipher the genetic basis of antidepressant response, although recent attempts have been made [21,22].

1.3. Pharmacogenetics of MDD

Though there are several options for treating MDD, antidepressant medications remain widely prescribed and the use of these medications has risen dramatically since the early 1990s [23,24]. At present, the trial-and-error process used to find effective medications for each patient is highly inefficient at every level, with more than 50% of antidepressant-treated patients failing to ever reach full remission [25]. While full remission is the ultimate goal of antidepressant treatment, response without remission often occurs, and although it is associated with a less favourable outcome, antidepressant response (50% reduction in symptoms) is the chosen phenotype for many studies [26]. Pharmacogenetic studies show that genetic variation significantly influences response to antidepressant medication and individual differences in drug response are often attributed to genetic variation [27–29]. An important feature of MDD is the diminished ability of the HPA axis to modulate stress response via cortisol [30]. Genetic studies show that variation in HPA axis genes significantly influence treatment success (e.g., Stamm et al. [31]). However, individual differences in response are not fully explained by genetic variation alone and while genetic studies of medication response have been invaluable, the field of pharmacogenetics has yet to fully account for why so many patients