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Review Article

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Literature Review on Pathogenesis and Treatment of Depression

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ABSTRACT

***Background:** Among various psychiatric disorders, depression is one of the most frequently encountered in today's world. Depression confers a significant risk of recurrence in the subsequent years following the first episode. In order to deal this disorder, it is crucial to comprehend the pathogenesis and properly implement the available management options. **Objectives:** We intend to explore the pathogenesis and patho-physiology of depression and highlight the available methods to treat and manage this psychiatric disorder including both pharmacotherapy and psychotherapy. **Methods:** A review of relevant articles published from 1988 till date in English language was done using the electronic databases of PubMed, Pico and, Google Scholar with preset keywords. **Conclusion:** Depression is a highly prevalent psychiatric disorder that requires a multidimensional approach. The pathogenesis of depression comprises of 30-40% genetic contribution and about 60-70% environmental factors. Environmental factors include stressful life events at any point in an individual's lifetime and alter the stress response by the hypothalamic-pituitary-adrenal axis. The patho-physiology of depression involves altered brain structure and function in addition to modified levels of neurotransmitters. Serotonin and its precursor tryptophan are decreased in the brain in depression in addition to various changes in catecholamines i.e. dopamine and norepinephrine. The treatment of depression is recommended by a combination of psychotherapy and pharmacotherapy which has higher efficacy than either therapy alone. The preferred forms of psychotherapy include interpersonal psychotherapy and cognitive behavioral therapy. The most commonly used pharmacotherapy include SSRIs, which are the most efficacious and tolerable antidepressants while other second generation antidepressants such as SNRI, TCA and MOA inhibitors, mirtazapine and trazodone are chosen on the basis of patient preference, cost, comorbidities and side effect profile.*

Key words: *Depression, pathogenesis, etiology, pathophysiology, genetic and environmental factors, cognitive behavioral therapy, pharmacotherapy.*

INTRODUCTION

Depression is a fairly common disorder and is one of the greatest causes of disease-associated disability and all-time mortality around the globe. [1] Based on the data collected from community-based surveys conducted in 14

different countries of the world, the lifetime prevalence of depression is said to be as high as 12 percent. [2] Depression is a common disease with substantial morbidity and mortality. When considering the population of people with major depression, it was estimated to be approximately 5% at any given time, and the percentage of experiencing a lifetime risk was higher in women (20-25%) compared to men (7-12%). Since today over 350 million people suffer from depression, the higher the cost of care ($59 billion in 2006), the higher the value loss from work and potential income loss due to suicide. A survey was conducted by World Mental Health in 17 countries and concluded that when the previous year number of episodes of depression was evaluated, on average about 1 in 20 people reported having an episode of depression. [3] Although depression affects both men and women, it is commoner in women causing as high as 50% burden in them irrespective of their socioeconomic status or income per capital ratio of their countries. [4] According to WHO, they define depressive disorder as a form of mental disorder which is all-encompassing and characterized by loss of interest and enjoyment, low mood and reduced energy that subsequently results in a state of increased fatigability with associated diminished activity. When evaluating various form of emotional problems, depression was ranked high and often affected ones are adolescents during this stage of development and it is characterized by worthlessness, inappropriate guilt or regret, hopelessness, and confused thinking. The management of depression is complicated due to patient inability to express how they feel making it difficult for the physician to fully assess the patient for depressive signs and symptoms and this is a big obstacle to care especially in the primary healthcare settings. Some are reluctant, keep a depressed mood and complaints are different from what they exhibit as physical signs. [3] The dangers associated with depression are evidence that recognizing, understanding, and treating depression are extremely important. [5] In order to manage this condition, it is mandatory for health care professionals to be aware of the complex pathogenesis of this disorder and manage this disorder with a tailored approach best suited to the needs and preferences of the individual patient.

MATERIAL AND METHODS

This literature review was conducted using the electronic biomedical databases of Google Scholar and PubMed Pico. We included studies published after the year of 1988 till date in English language. Keywords used to search through the databases were depression, unipolar major depression, pathogenesis, etiology, pathophysiology, genetic and environmental factors, psychotherapy, cognitive behavioral therapy, pharmacotherapy, and selective serotonin reuptake inhibitors.

We employed no software for analyzing the results obtained from the review of published articles. However, to ensure that the data compiled is free of error and valid, multiple revisions were done by each of the authors.

DISCUSSION

The prevalence of major depression and depressive symptoms has followed an incremental trend in the past decades. [6] It is estimated that the lifetime prevalence of major depression is higher in women than in men with rates as high as 25% reported in women and up to 12% reported in men. [7] Depression can significantly impact the quality of life of an individual and its management can be quite challenging.

The etiology and pathophysiology of unipolar major depression are quite complex and mostly based on neurobiological findings in clinical psychiatry. Depression is thought to be the outcome of interplay between genetic factors and environmental factors. Genetic factors contribute about 30-40% to the pathogenesis of depression; while, the remaining susceptibility is attributed to environmental factors i.e. 60-70% which are unique to every individual. [6] Genetic predisposition of depression can be inherited by an individual; however, gene expression may be altered at any point in brain development as a result of stress from non-genetic environmental factors. [7] In a large scale meta-analysis, the genetic predisposition of depression was assessed in over 21,000 individuals and a concordance rate of as high as 37 percent was discovered in monozygotic twins. [8] The role of genetic factors in the development of depression is even stronger in females when compared to males. [8] Although the role of genetic factors in the pathogenesis of depression has been unanimously proven, several genome-wide association studies (GWAS) have failed to identify specific genes or link specific loci to the development of depression, possibly explained by the marked heterogeneity of depression. [9, 10]

Environmental factors are crucial to the development of major unipolar depression. Stressful events that occur in the early life of a person such as childhood trauma can predispose an individual to the risk of depression as a result of increased sensitivity to stress and a modified response to stimuli. [11] The association between stressful

events and depression can be explained by the heightened activity of hypothalamic corticotropin-releasing factor cells in response to early life stress that subsequently increases stress responses for the entire lifetime. This modified hypothalamic-pituitary-adrenal stress response not only persists for the entire lifetime of an individual but can be transmitted genetically to the subsequent generations. [12] Apart from childhood trauma, stressful life events that occur at any point in the lifetime of an individual can render susceptibility to depression. This observation is evidenced in a prospective study by Assari et al. that proved that the risk of developing major depression after experiencing a stressful life event lasting for up to 25 years after the event with an odds ratio of 1.41. [13] In contrary, another study found the association between stressful life events and depression to last for only one month after the occurrence of the event. [14] Regardless of the duration that the risk lasts, the fact that stressful life events predispose to depression is undeniable based on several studies. Apart from genetic and environmental factors, several social factors contribute to the pathogenesis of depression including social isolation, poor social and emotional support, social harassment of any kind, negative criticism or undue emotional over-involvement from friends or family members, as well as depression in friends or neighbors. [15, 16]

The pathophysiology of depression comprises an alteration in both the structure as well as the function of the brain. The overproduction of corticotropin-releasing hormone leads to overactivation of the hypothalamic-pituitary-adrenal axis in several patients with depression. [17] The anatomic changes in the brain in depression include a reduction in the size of the hippocampus, decreased volume of the frontal lobe and increased ventricular-brain ratio. [18, 19] Furthermore, neurotransmitters play a significant role in the pathophysiology of depression including diminished levels of monoamines, especially serotonin and norepinephrine. [20] Serotonin is critical in the development of depression and has been shown to be decreased in the brains of depressed individuals by several retrospective and prospective studies. [21] In addition to serotonin, its precursor tryptophan also exists at lower levels in the brain in depression. [21] Catecholamines including both dopamine and norepinephrine have also been associated with depression. [22] Additionally, other neurotransmitters may be abnormal in depression such as altered levels of GABA and glutamate in various regions of the brain such as occipital lobe and the prefrontal cortex can be expected. [23]

The management of depression is multidimensional and requires extensive attention and patience on the part of the physician. The mainstay of the treatment of depression is psychotherapy and pharmacotherapy. A combined approach consisting of both psychotherapy and pharmacotherapy is preferred over the use of either therapy alone due to superior outcomes of the combined approach in multiple clinical trials. [24, 25] The most commonly recommended psychotherapies that are effective in the treatment of depression include problem-solving therapy, behavioral activation, family and couples therapy, supportive psychotherapy, psychodynamic psychotherapy, interpersonal psychotherapy and Cognitive-behavioral therapy (CBT). [26, 27] Several studies have demonstrated that the various types of psychotherapy are similar to one another in terms of efficacy and outcomes; [28] hence, the type of psychotherapy chosen can be tailored to the individual needs and preferences of the patient as well as the availability of resources. The most widely studied forms of psychotherapy are CBT and interpersonal psychotherapy and extensive evidence exists for their efficacy, thereby, these two types of psychotherapy are often recommended as the initial approach in addition to pharmacotherapy. [29]

The initial treatment of unipolar major depression includes pharmacotherapy in the form of antidepressants in addition to psychotherapy. Among the wide variety of available antidepressants, selective serotonin reuptake inhibitors (SSRIs) have shown the best efficacy and tolerability in several randomized clinical trials and meta-analyses and are therefore the most commonly prescribed type of antidepressants today. [30, 31] This is evident from a large scale meta-analysis that compared various types of antidepressants in over 26,000 patients with depression that concluded the most effective antidepressants to be SSRIs, specifically escitalopram and sertraline based on the highest number of subjects that displayed a reduction in baseline symptoms ≥50 percent. [32] Reasonable alternatives to SSRIs for the treatment of depression include other antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (CAs), monoamine oxidase inhibitors (MOA) and atypical anti-depressants such as mirtazapine and bupropion. While SSRIs are superior in efficacy to all other antidepressants, other classes have comparable efficacy as shown by several trials and no one is superior to another. [33-35] The specific antidepressant used for treatment is therefore tailored to the patient's preferences, side-effect profile, comorbidities and other coexisting conditions, cost and affordability, drug-drug interactions, and patient or relative's response to a particular antidepressant. For example, escitalopram and citalopram are less likely to cause drug-drug interactions, bupropion is preferred in the patients

who desire treatment of tobacco use or want to avoid sexual dysfunction, and mirtazapine has a very rapid onset of action and is avoided in the patients who want to avoid weight gain. [36, 37]

Some side effects such as gastrointestinal toxicity are seen in all second-generation antidepressants; while, other side-effects occur with the specific use of some classes. [34] The most commonly observed adverse effects associated with SSRIs include diarrhea and sexual dysfunction. SNRIs such as venlafaxine and desvenlafaxine are associated with nausea and vomiting. Weight gain is seen most commonly with the use of mirtazapine; while, somnolence is a significant side-effect of trazodone. Several antidepressants including SSRI, SNRI, and TCAs have been linked to liver injury in the form of elevated serum aminotransferases and in some cases, the liver injury is severe enough to cause liver failure and requires liver transplantation. [38] Antidepressants have also been linked to stroke by a retrospective analysis. [39] Additionally, antidepressants have been linked to an increased risk of diabetes by several studies such as a comparative study that reported an incidence rate ratio of 1.8 of diabetes with the use of antidepressants. [40]

CONCLUSION

One of the commonest mental disorders presenting categorically with depressed mood is depression. There is also associated loss of interest or pleasure, feelings of guilt or low self-worth, decreased energy, loss of appetite or even disturbed sleep in some scenarios, and poor concentration in others. Most depressed patients also show anxiety which can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide. Based on the findings of this literature review, depression which is a frequently encountered psychiatric disorder occurs because of a combination of genetic and environmental factors. The pathophysiology involves altered brain structure and function in addition to altered levels of neurotransmitters especially serotonin. The treatment of depression is commonly done by a combination of psychotherapy and pharmacotherapy. The preferred forms of psychotherapy are interpersonal psychotherapy and cognitive behavioral therapy; while, the most commonly used medications include SSRIs, SNRI, TCA and MOA inhibitors. The burden of depression and other mental health conditions is on the rise globally; depression is a leading cause of disability and has been projected to become the 2nd most burdensome disease by the year 2020. Therefore, more research that enlightens and promote awareness should continue to be done on this disease.

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