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Review Paper

Depression – A Review

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Abstract

Major depression is a mood disorder characterized by a sense of inadequacy, despondency, decreased activity, pessimism, anhedonia and sadness where these symptoms severely disrupt and adversely affect the person's life, sometimes to such an extent that suicide is attempted or results. The search for an extended understanding of the causes of depression, and for the development of additional effective treatments is highly significant. Clinical and pre-clinical studies suggest stress is a key mediator in the pathophysiology of depression.

Keywords: Depression, neurotransmitters, stress, treatment, anti depressants

Introduction

As estimated by WHO, depression shall become the second largest illness in terms of morbidity by another decade in the world, already one out of every five women, and twelve men have depression. Not just adults, but two percent of school children, and five percent of teenagers also suffer from depression, and these mostly go unidentified. Depression has been the commonest reason why people come to a psychiatrist, although the common man's perception is that all psychological problems are depression[1-2]. What one sees in most patients is the myth related to depression. People still believe that it is because of some weakness in personality, or that one can cure it by oneself, or that medication would go lifelong and are mere sedatives.

All these are myths, and mostly created by faith healers, or unqualified counsellors, and non-medical experts for their own vested interest, and largely by an unaware of society. An increased awareness, and approach to psychiatrists, has been the main reason for the increase in number of patients and not necessarily an increase in prevalence. With newer medication, and better facilities, treating depression has become easier, and most people respond very well to treatment, and return to optimum functioning very soon[3].

Types of depression: Depressive illness comes in different forms, just as many other illnesses: i. Major depression is manifested by a combination of symptoms that interfere with the ability to work, sleep, eat and enjoy once pleasurable activities. These disabling episodes of depression can occur once, twice or several times in a lifetime. ii. Dysthymia, a less severe type of depression, involves long-term, chronic symptoms that do not disable, but keep you from functioning at "full steam" or from feeling good. Sometimes people with dysthymia also experience major depressive episodes. iii. Manic-depressive or bipolar is not nearly as prevalent as other forms of depressive illnesses. It involves cycles of depression and elation or mania. Sometimes the mood switches are dramatic and rapid, but most often they are gradual. When in the depressed cycle, one can have any or all other the symptoms of a depressive illness. When in the manic cycle, any or all symptoms listed under mania may be experienced. Mania often affects thinking, judgment, and social behaviour in ways that may cause serious problems and embarrassment[4-5].

Prevalence – World scenario and Indian scenario

Indian: Depression is the most common psychiatric disorder reported in most of the community based studies. It is also reported as one of the most common psychiatric disorder in outpatient clinic population and in subjects seen in various medical and surgical setting. It is also reported to be the most common psychiatric disorder in elderly subjects across various settings. Studies from India have also shown that life events during the period preceding the onset of depression play a major role in depression. (Table-1) Studies on women have also shown the importance of identifying risk factors like interpersonal conflicts, marital disharmony and sexual coercion[6-7].

There is need for further study of factors like cost, attitude towards treatment, adherence, compliance and neurobiological correlates. There is also a need to study the course of depressive disorders in India so as to determine the need and duration of continuation treatment. Studies should also evaluate the cost-effective models of treatment which can be easily used in the primary care setting to effectively treat depression[8].

Table-1
The Indian Council of Medical research, a collaborative project at four centres (Bikaner, Goa, Patiala and Vellore) and the outcome[9]

ICMR descriptive Categories	*Bikaner N=68 %*	*Goa N=85 %*	*Patiala N=102 %*	*Vellore N=68 %*	*All centres N=323 %*
Predominantly Depressed type	5.9	11.8	17.7	11.8	11.8

World

Table-2
Total population effects of different depression interventions are reported in given above Table[10]

	Africa		**The Americas**			**Eastern Mediterranean**		**Europe**			**South-East Asia**		**Western Pacific**	
	AfrD	AfrE	AmrA	AmrB	AmrD	EmrB	EmrD	EurA	EurB	EurC	SearB	SearD	WprA	WprB
Total population (million)	294.1	345.5	325.2	430.9	71.2	139.1	342.6	411.9	218.5	243.2	293.8	1241.8	154.4	1532.9
Current burden of depression	1906	2154	5031	5589	867	1184	3507	4074	2548	2634	2832	17 123	1000	14 515

Symptoms of depression: Not everyone who is depressed or manic experience every symptom. Some may experience a few symptoms, some many. Also, the severity of symptoms may vary with individuals[11-14].

Depression: i. persistent sad, anxious or empty mood, ii. feelings of hopelessness, pessimism, iii. feeling of guilt, worthlessness, helplessness, iv. loss of interest or pleasure in hobbies and activities that you once enjoyed, including sex, v. insomnia, early-morning awakening or oversleeping, vi. appetite and or weight loss or overeating and weight gain, vii. decreased energy, fatigue, being slowed down, viii. thoughts of death or suicide, suicide attempts, ix. restlessness, irritability, x. difficulty concentrating, remembering or making decisions, xi. persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders and chronic pain

Causes of disease – Environmental factors and Gene component

Genetic Causes of Depression

Most of the published genetic association studies of mood disorders have focused on functional polymorphisms (DNA sequence variations that alter the expression and/or functioning of the gene product) in the loci encoding the serotonin transporter (SLC6A4), serotonin 2A receptor (5HTR2A), tyrosine hydroxylase (TH) (the limiting enzyme for dopamine synthesis), tryptophan hydroxylase 1 (TPH1) (serotonin synthesis), and catechol-o-methyltransferase (COMT) (dopamine catabolism[15].

It has long been known that depressive illnesses can run in families, but until fairly recently it was not fully known whether people inherited a susceptibility to these illnesses or if something else such as the environment was the true culprit. Those who research depression have been able to determine that to some extent depressive illnesses can be inherited. What appears to be inherited is a vulnerability to depression. This means that if we have close relatives who have clinical depression, we may inherit a tendency to develop the illness. It does not mean that we are destined to become depressed[16-17].

Bipolar disorder has a strong genetic influence. Of those with bipolar disorder, approximately 50% of them have a parent with a history of clinical depression. When a mother or father has bipolar disorder, their child will have a 25% chance of developing some type of clinical depression. If both parents have bipolar disorder, the chance of their child also developing bipolar disorder is between 50% and 75%. Brothers and sisters of those with bipolar disorder may be 8 to 18 times more likely to develop bipolar disorder, and 2 to 10 times more likely to develop major depressive disorder than others with no such siblings[18].

Twin Studies: Much of what we know about the genetic influence of clinical depression is based upon research that has been done with identical twins. Identical twins are very helpful to researchers since they both have the exact same genetic code. It has been found that when one identical twin becomes depressed the other will also develop clinical depression approximately 76% of the time. When identical twins are raised apart from each other, they will both become depressed about

67% of the time. Because both twins become depressed at such a high rate, the implication is that there is a strong genetic influence. If it happened that when one twin becomes clinically depressed the other always develops depression, then clinical depression would likely be entirely genetic. However because the rate of both identical twins developing depression is not closer to 100% this tells us that there are other things that influence a person's vulnerability to depression. These may include environmental factors such as childhood experiences, current stressors, traumatic events, exposure to substances, medical illnesses, etc[19].

Research has also been done with fraternal twins. Unlike identical twins that have the same genetic code, these siblings share only about 50% of their genetic makeup and do not necessarily look alike. Studies have shown that when one fraternal twin becomes depressed, the other also develops depression about 19% of the time. This is still a higher rate of depression when compared to overall rates for the general public, again pointing towards a genetic influence in the development of clinical depression[20-21].

Environmental Causes of Depression

Environmental causes of depression include events such as stress, traumatic events and childhood difficulties. These are events that can happen to anyone and they happen during our everyday lives. They are considered factors that are outside of us. Some researchers refer to these events as sociological or psychosocial factors because they are a "meeting" or "combination" of events that happen in society and the function and workings of the human mind. Researchers have known for some time that the experiences (events) we have in our lives can and do affect our mental health. Thoughts, emotions and behaviours of people are influenced by the prior experiences in their lives. These experiences can include past relationships, childhood development and past crises. The key to development of clinical depression in some people seems to be how they react to the various environmental causes or factors in their everyday lives[22].

Stress: There appears to be a very complex relationship between stressful situations, the reaction of the individual's mind and body to stress, and the development of clinical depression. Most researchers believe that for some people there is a direct relationship between a stressful event and the development of depression. What is interesting to note is that this stress can be negative or positive. Examples of negative stress are loss of a loved one, loss of a job, loss of a relationship and divorce. Examples of positive stress are planning for a wedding, preparing for a new job, and moving to a new city. Both negative and positive stress from environmental events can precede the development of depression[23].

Traumatic Events: It is a fact that many people have experienced a traumatic event prior to developing depression. Traumatic events in the lives of people include loss of a loved one, a serious medical illness, the end of a marriage or significant financial loss. These types of events can destroy the sense of control and stability in a person's life, often leading to emotional distress[24].

Childhood Difficulties: It has long been known that people with severe difficulties in childhood have higher rates of clinical depression. The most common childhood difficulties include sexual, emotional, or physical abuse, disfunctional upbringing, parental separation, and mental illness in one or both of the parents. One of the most difficult emotional events for a child to endure is the separation or death of a parent before the age of eleven[25-26]. Children that have experienced this event also demonstrate a higher probability of developing depression.

Synthetic Chemicals: Every day we take in synthetic chemicals from all over. From preservatives, additives and hormones that are found and added to so many of our foods, pesticides that are sprayed and air and water pollution as well. Studies have shown that air and water pollution alone can cause cancer and other diseases. Synthetic chemicals and pollutants are now being more closely looked at as a link to depression and Major Depressive episodes[27].

Noise Pollution: Noise pollution has been linked to aggression, hypertension, increased stress levels, tinnitus, hearing loss and disruptions in sleep. Specifically, tinnitus is linked to severe depression, panic attacks and forgetfulness. Continual exposure to noise pollution has also been linked to cardiovascular disease and increased blood pressure. A person with possible depressive tendencies will become even more susceptible to depression with continual, prolonged exposure to noise pollution[28].

Electrical Pollution: We are constantly surrounded by radio waves everywhere we go. Much of the electrical equipment we use works off of radio waves and these radio waves have been found to induce depression and rage. The exact causes as to why are not yet known and unlike other types of environmental causes of depression, electrical pollution cannot be seen, heard, tasted, or felt. But, it does have a negative effect on our mind and body[29].

Natural and Catastrophic Disasters: Natural and catastrophic disasters, such as hurricanes, earthquakes, or fires, and even manmade disasters such as bombings and war can push an already susceptible person into a severe Major Depression[30]. The National Centre for Environmental Health has found that people, who normally would not be a candidate for depression, can become depressed after major life altering episodes, such as their house being destroyed in a natural disaster[31].

Treatment

Mild depression can be effectively treated with either medication or psychotherapy. Moderate to severe depression may require an approach combining medication and psychotherapy[32].

Drug Treatment: 50-65% of patients respond to the first antidepressant. No particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patients' symptoms to side effect profile, presence of medical and psychiatric co morbidity, and prior response. Relative costs can also be considered (e.g., generics). UMHS preferred agents are Fluoxetine (generic) and citalapram (Celexa ®)[33]. Patients treated with antidepressants should be closely observed for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose increases or decreases.

The therapeutic effects of antidepressants are believed to be caused by their effects on neurotransmitters and neurotransmission. The Monoamine Hypothesis is a biological theory stating that depression is caused by the under activity in the brain of monoamines, such as dopamine, serotonin, and norepinephrine. In the 1950s the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants were accidentally discovered to be effective in the treatment of depression. These findings and other supporting evidence led Joseph Schildkraut to publish his paper called "The Catecholamine Hypothesis of Affective Disorders" in 1965. Schildkraut associated low levels of neurotransmitters with depression. Research into other mental impairments such as schizophrenia also found that too little activity of certain neurotransmitters were connected to these disorders[34,35,36]. The hypothesis has been a major focus of research in the fields like pathophysiology and pharmacotherapy for over 25 years.

Monoamine oxidase inhibitors (MAOIs) block the degradation of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine by inhibiting the enzyme monoamine oxidase, leading to increased concentrations of these neurotransmitters in the brain and an increase in neurotransmission[37].

Tricyclic antidepressants (TCAs) prevent the reuptake of various neurotransmitters, including serotonin, norepinephrine, and to a much less extent, dopamine. Nowadays the most common antidepressants are selective serotonin reuptake inhibitors (SSRIs), which prevent the reuptake of serotonin (thereby increasing the level of active serotonin in synapses of the brain). Other novel antidepressants affect norepinephrine reuptake, or different receptors on the nerve cell[38,39,40].

While MAOIs, TCAs and SSRIs increase serotonin levels, others prevent serotonin from binding to 5-HT_{2A} receptors, suggesting it is too simplistic to say serotonin is a happy hormone. In fact, when the former antidepressants build up in the bloodstream and the serotonin level is increased, it is common for the patient to feel worse for the first weeks of treatment. One explanation of this is that 5-HT_{2A} receptors evolved as a saturation signal (people who use 5-HT_{2A} antagonists often gain weight), telling the animal to stop searching for food, a mate, etc., and to start looking for predators[41]. In a threatening situation it is beneficial for the animal not to feel hungry even if it needs to eat. Stimulation of 5-HT_{2A} receptors will achieve that. But if the threat is long lasting the animal needs to start eating and mating again - the fact that it survived shows that the threat was not as dangerous as the animal felt. So the number of 5-HT_{2A} receptors decreases through a process known as down regulation and the animal goes back to its normal behaviour. This suggests that there are two ways to relieve anxiety in humans with serotonergic drugs: by blocking stimulation of 5-HT_{2A} receptors or by over stimulating them until they decrease via tolerance[42-43].

The stimulation or blocking of different receptors on a cell affects its genetic expression. Recent findings have shown that neurogenesis, and thus, changes in brain morphogenesis, mediate the effects of antidepressant drugs.

Another hypothesis is that antidepressants may have some longer-term effects due to the promotion of neurogenesis in the hippocampus, an effect found in mice. Other animal research suggests that antidepressants can affect the expression of genes in brain cells, by influencing "clock genes"[44-45].

Other research suggests that delayed onset of clinical effects from antidepressants indicates involvement of adaptive changes in antidepressant effects. Rodent studies have consistently shown up regulation of the 3, 5-cyclic adenosine monophosphate (cAMP) system induced by different types of chronic but not acute antidepressant treatment, including serotonin and norepinephrine uptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, lithium and electroconvulsions. cAMP is synthesized from adenosine 5-triphosphate (ATP) by adenylyl cyclase and metabolized by cyclic nucleotide phosphodiesterases (PDEs)[46-47]. Data also suggest that antidepressants can modulate neural plasticity in long-term administration.

One theory regarding the cause of depression is that it is characterized by an overactive hypothalamic-pituitary-adrenal axis (HPA axis) that resembles the neuro-endocrine (cortisol) response to stress. These HPA axis abnormalities participate in the development of depressive symptoms, and antidepressants serve to regulate HPA axis function[48,49,50].

Frequent Initial Visits: Patients require frequent visits early in treatment to assess response to intervention, suicidal ideation, side effects, and psychosocial support systems.

Continuation Therapy: Continuation therapy (9-12 months after acute symptoms resolve) decreases the incidence of relapse of major depression. Long term maintenance or life-time drug therapy should be considered for selected patients based on their history of relapse and other clinical features[51-52].

Education/Support: Patient education and support are essential. Social stigma and patient resistance to the diagnosis of depression continue to be a problem[52].

Side effects for Prolong Treatment

The antidepressants are crucial for the treatment of depressive episodes in the acute phase when untreated symptoms are at their worst. With long-term use, however, the brain sets to work compensating for the drug-induced changes with a process he calls oppositional tolerance. The brain tries to re-establish its usual balance of production, release and reuptake of neurotransmitters – as every system of the body does when its normal functioning has been disturbed. The idea is that if the medication artificially jacks up the brain's level of serotonin or norepinephrine, the neurobiology of the system reacts by reducing its own production of the neurotransmitter. In other words, if antidepressant use continues long enough, the brain will create a system to cancel out its effect. There is a possibility that antidepressant use itself could be causing the problem[53]. There are specific neurobiological reactions that could account for the emergence of higher levels of resistance to treatment. In addition, there is evidence that stopping antidepressants in people who no longer respond to them can lead to reversal of symptoms as the brain compensates once more, this time for the withdrawal of the drugs. For some people, however, stopping the medication has no effect. They continue to have recurring depression. If antidepressant treatment is restored as a response, these patients can develop a permanently recurring illness. This is tardive dysphoria[54,55].

Alternative Treatments for Depression

There is no evidence that any alternative treatment or home remedy is effective in treating moderate to severe depression. However, some people with mild depression may find benefit from home remedies through increased relaxation.

Relaxation can provide relief from depressive symptoms. It can also help cope with some of the causes of depression, such as grief, anxiety, changing roles, and even physical pain. If you have depression and are considering using an alternative form of therapy, it is important to seek the advice of the health care provider[56].

Examples of alternative therapies include: Acupuncture, Aromatherapy, Biofeedback, Chiropractic treatments, Guided imagery, Herbal remedies, Hypnosis, Massage therapy, Meditation, Relaxation, Yoga, etc[57].

Meditation is sometimes described as an altered state of consciousness. It is a form of relaxation that, unlike sleep, is entered into purposely. Meditation is usually practiced regularly for at least 10 minutes each day. While the body is at rest, the mind is cleared by focusing on one thought -- sometimes a word, a phrase, or a particular scene.

Relaxation is marked by decreased muscle tension and respiration, lower blood pressure and heart rate, and improved circulation. The relaxation response summoned by meditation slows down the sympathetic nervous system. In addition to slowing the heart rate and lowering blood pressure, this response can also lead to: i. Decreased sweat production, ii. Decreased oxygen consumption, iii. Decreased catecholamine production (chemicals associated with the stress response). iv. Decreased cortisol production (stress hormone)[58].

Different forms of exercise can lower stress, relax you, and reduce depression. Exercise can also increase your energy, balance, and flexibility. In general, exercise is a safe, effective, and easy way to improve your well-being.

Music therapy has been shown to be an effective non-drug approach for people of all ages that assist in reducing fear, anxiety, stress, or grief. Music can be thought of as a natural tranquilizer for the human spirit. Pythagoras, the sixth century B.C. philosopher and mathematician, is thought to have been the founder of music therapy. During World War II, the Veterans' Hospitals had volunteers who played their music for the wounded soldiers. The results were so positive that the VA added music therapy programs. In its simplest form, all you need to incorporate music therapy is a CD player or mp3 player with headphones. Then choose music -- from New Age "mood" music to rock to classical -- that matches your personal needs, moods, and tastes.

Application of Modern Technology for Diagnosis and Treatment – Under Development - Hypothesis

The search to find safer, more effective and more rapidly acting antidepressants that might also benefit currently treatment-resistant patients continues unabated.

Major progress in new antidepressant development has been slow, with the notable exception of a group of serotonin selective reuptake inhibitors (SSRIs) introduced in the last 5 years. Although the SSRI's therapeutic effects are accompanied by fewer serious side effects and over dosage hazards than the first- and second-generation antidepressants, their principal mechanism of action, neurotransmitter uptake inhibition, is certainly not a novel one[59].

Before considering specific drug classes, several criteria need to be considered. Discussion of the pharmacological treatment of depression depends on what patients are subsumed under this broad diagnostic category and what assessment measures and criteria are accepted as indicating a meaningful antidepressant effect. Diagnostic criteria employed in many recent outpatient studies yield populations that sometimes show a high (>50%) 6-week placebo response rate, requiring large numbers of subjects (over 100) to demonstrate significant therapeutic advantage over placebo for a new, active antidepressant. In these populations, even such established antidepressants as imipramine sometimes do not emerge as clearly superior to placebo. European and some U.S. studies of potential antidepressants that are based on

comparisons with standard tricyclics alone often may reveal no difference, suggesting equal efficacy for the new drug. However, judgment may need to be reserved as to claims of efficacy when adequate comparisons with a placebo group are unavailable. Possible differences in the clinical characteristics of patients studied in U.S. versus European settings must also be taken into account in assessing response data. In addition, some psychotherapeutic agents such as alprazolam and trazodone have sometimes uncritically been referred to as antidepressants in the broad sense that is they have been reported to be equivalent to first generation tricyclic or other antidepressants in some studies and thus, by implication, considered equally effective in severely depressed, nonpsychotic hospitalized patients. It is doubtful whether most experienced clinicians would consider using alprazolam or trazodone as the mainstay treatment for a patient so dysfunctional with depression as to require hospitalization. On the other hand, recent comparisons provide difficult-to-ignore evidence that certain agents [e.g., the irreversible monoamine oxidase (MAO) inhibitors] may be superior to tricyclic antidepressants in subgroups of depression such as bipolar or atypical depression. All of this highlights a level of uncertainty about selecting and evaluating novel pharmacological approaches for treating patients with depression and allied disorders[60].

One possible organizing principle to survey potential novel antidepressants would be to select compounds on the basis of their activity in animal models sensitive to antidepressant drug effects. However, this approach does not answer the question, because many animal models have multiple limitations for identifying novel antidepressants, ranging from circularity (e.g., the test merely reflects a biochemical property of standard drugs) to failure to detect any activity of certain established agents (e.g., inability of the MAO inhibitors to reverse passive avoidance deficits). Although some widely used behavioural paradigms (for example, the learned helplessness paradigm, the forced swim test, and the restraint stress-induced reduction of locomotor activity) yield positive results for most currently used antidepressant drugs, false positives and false negatives have been found for some novel compounds. Only clinical testing can definitively establish the utility of a new compound in the treatment of depression, whether narrowly or broadly defined, and a strong case can be made for clinical serendipity being involved in the discovery of most effective antidepressant agents thus far identified. Ultimately, we must depend on the observations of skilled clinicians employing well-targeted populations to find truly novel antidepressants with distinct efficacy in areas of need, rather than on drug–placebo differences established solely in large trials with relatively fewer impaired outpatients[61,62].

In a study done, it was demonstrated that the antidepressant-like effect of the acute administration of Withaferin-A, is linked to the modulation of nNOS. Pre-treatment of rat with sub effective doses of nNOS inhibitor and Withaferin-A produced an antidepressant-like effect. Withaferin-A has been shown to be superior in efficacy to selective 5-HT reuptake inhibitors (SSRIs) in severe major depressive disorder, treatment-resistant depression and obsessive compulsive disorder. Various behavioural, biochemical and molecular studies are being carried out to elucidate the exact mechanism of the antidepressant effect of Withaferin-A. The study demonstrates that the pre-treatment of rat with different nNOS inhibitors produces an antidepressant-like action with a sub effective dose of Withaferin-A. However, more studies are necessary to elucidate the molecular mechanisms of Withaferin-A action in nNOS, as well as other mechanisms that may be involved in its antidepressant-like activity[63].

Conclusion

Depression is a serious medical condition and a profound public health concern. Although the development of depression is likely due to a combination of factors, understanding the effects, possible triggers, and treatments of the disorder is essential for promoting the well being of affected individuals. There is also a need to study the course of depressive disorders present in the world so as to determine the need and duration of continuation treatment. Studies should also evaluate the cost-effective models of treatment which can be easily used in the primary care setting to effectively treat depression.

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