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Review Paper on Depression

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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 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.

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INTRODUCTION

Depression is a serious disorder in today's society, with estimates of lifetime prevalence as high as 21% of the general population in some developed countries (1). As defined by the American Psychiatric Association (2), depression is a heterogeneous disorder often manifested with symptoms at the psychological, behavioral and physiological levels (Box 1). As with all diseases, approximations of both the disorder and the actions of corrective medications in laboratory animals are essential for the development of effective therapies. The wide spectrum of disruptions that characterize depression highlights the difficulty of posing researchers to mimic the disorder in the laboratory. Indeed, two human symptoms, recurring thoughts of death or suicide, or excessive thoughts of guilt, are impossible to model in laboratory animals. The question remains impenetrable as to whether we can ever know whether a laboratory animal is 'depressed'(Fig. 1). Nonetheless, numerous attempts have been made to create animal models of depression, or at least of the symptoms of depression, and criteria for their evaluation have been established. Some of the most widely cited criteria were developed by McKinney and Bunney >30 years ago (3). They proposed that the minimum requirements for an animal model of depression are: (a) it is 'reasonably analogous to the human disorder in its manifestations or symptomatology; (b) there is a behavioral change that can be monitored objectively; (c) the behavioral changes observed should be reversed by the same treatment modalities that are effective in humans; and (d) it should be reproducible between investigators. Most models of depression in use at that time were based on primate separation experiments that attempted to model the entire syndrome of depression. However, subsequent efforts to delineate validity criteria for animal models often do not take into account the reliability and usability of the paradigm in the everyday rodent laboratory setting and are often based on esoteric, theoretical principals rooted in comparing the etiological basis between the human condition and the syndrome in the animal model (4), but also see (5). Unlike other medical disorders where the pathology is well defined, such as diabetes or Parkinson's disease, the underlying pathophysiology of depression is still unresolved, thus making it virtually impossible to fulfill criteria solely based on etiology. Most recently, it has become clear that a more useful strategy might be to model single endophenotypic differences (i.e. one clear-cut behavioral output) relevant to the disease state as opposed to a syndrome (4). Geyer and Markou (4) have proposed that the only criteria that are necessary and sufficient for initial use are that the paradigm has strong predictive validity

and that the behavioral readout is reliable and robust in the same laboratory and between laboratories.

Figure no 1. Rat Depression

Figure no. 1. A 'depressed' rat? It is an impossible quest to mimic major depressive disorders completely in rodents. Instead of anthropomorphizing the human condition, as in the cartoon, investigators have developed paradigms that detect specific behavioral endophenotypic differences (clear-cut behavioral outputs) that are sensitive to the effects of antidepressant treatments (both pharmacological and non-pharmacological.

Box 1.Symptoms of major depression [a]

- Depressed mood most of the day (in children and adolescents, irritability might signify a depressed mood)
- Markedly diminished interest or pleasure in all or most activities most of the day
- Large increase or decrease in appetite
- Insomnia or excessive sleeping
- Psychomotor agitation (evident by, for example, hand wringing) or slowness of movement Fatigue or loss of energy
- Indecisiveness or diminished ability to think or concentrate
- Feelings of worthlessness or excessive or inappropriate guilt
- Recurrent thoughts of death or suicide

Reference an American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders (4th edn), American Psychiatric Press.

The causative agent for Depression-

Inflammation and mitochondrial oxidative processes generate free radicals, which are highly reactive species chemically. When these radicals become in excess or when the antioxidant system gets consumed, Reactive Oxygen Species (ROS) may react with macromolecules of the cell-like fatty acid, DNA, protein, etc thereby causing damage to these macromolecules. Brain, due to its high metabolic rate, is one of the most vulnerable organs to the damaging effects of ROS. This may explain ROS involvement in several neuropsychiatric diseases. ROS may play an active role in the pathophysiology of depression by various mechanisms such as tissue damage, inflammation, neurodegeneration, autoimmune mechanisms generated by tissue damage, apoptosis.

Given the increasing number of infections developing due to ROS, the effectiveness of the existing antioxidant molecules needs to be improved utilizing various approaches of drug design and synthesis. Although several antioxidant molecules exist which may be able to counteract with the ROS, still the pursuit of developing a highly potent antioxidant continues to date. A chemical compound which may be able to inhibit the ROS generated through many pathways is the need of the hour. Such molecules may not only be able to decrease the production of ROS but also will help the design of newer antidepressant molecules which lower unwanted effects (6).

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)(18).

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 behaviors 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 the 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 before 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, dysfunctional 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 hurt 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).

Patient factors:- Social and demographic factors that are associated with forgetfulness include low social and cultural levels and living in rural areas, as has been found in several reports (7,8,9). This suggests that the use of treatment is related both to the education level and with the accessibility to specialized care. It has been reported elsewhere that up to 50% of patients leave the physician's office without having fully understood the instructions provided for their treatment (10). Low income and low educational levels have been related to bad adherence in many papers (7,8,9). This must be related to other factors as difficulty to have access to specialized resources, to acquire treatment, lack of social support (that could aggravate per se the depressive symptomatology) and personal instability.

The problem of measure compliance:-

In the literature on this topic, figures for poor adherence to antidepressants, among patients with affective disorders, varies between 10-30% and 60% (11,12). These figures do not appear to have changed after the introduction of newer drugs, with reduced undesirable effects. A majority of physicians underestimate the problem of non-compliance. Despite the growing use of clinical guidelines, treatment algorithms, newer drugs with less adverse effects and other improvements in therapeutics, there continues to be a relevant difference between the efficacy of antidepressants seen in clinical trials and that seen in clinical practice. This difference may stem from a lack of information (13). Adherence seems to be directly related to a patient's awareness of having been told about a drug's adverse effects by their physician: the less they remember about it, the worse their adherence is. Also, it appears that there is a discrepancy between the instructions that physicians say they give to their patients and those that the patients recall being given (14). On average, poor compilers have been found to stop taking their medication after only 43 days, even if the response to the medication is positive. However, poor compliance is seen after only 15 days if they develop an adverse effect, after 20 days if their condition worsens, and after 40 days if the response is less than they expected (15). Psychiatrists tend to presume that non-adherence among patients with chronic depression is uncommon, and place it around 16% (17), lack of adherence waits in psychotic illness, but usually, we expect than people who are suffering depressive symptoms and come voluntarily to the consultation would follow prescriptions. However, when asked if they made any mistake in the way they took their medication the day before, 1 out of every 3 patients admits to having made some mistake, and 8% acknowledge that mistakes occur 'very often'. Aspects that have been shown to influence good use include the treatment's efficacy and the daily number of pills to be taken. Factors associated with good adherence include the presence of family members, emotional stability, and positive relationship with the physician, and a perceived improvement with the drug. However, adherence decreases as the duration of therapy lengthen. Other studies have found adherence to be as low as 39.7%, with older patients, and those with higher scores on the scale of chronic disease, having better adherence (16). Over 43% of patients do not comply with their long term treatments, and 75% fail to introduce the life habit changes recommended by their physicians (17).

Mortality associated with depression-

Surprisingly enough the data on the mortality risk associated with depression has shown mixed results in the past. This is in part because the mortality risk is difficult to analyze. The criteria used to define depression vary from study to study. Also, it is difficult to separate the effects of comorbid conditions. Medical conditions can lead to depression and depression can influence the outcome with medical conditions. The presence of other mental illnesses, substance abuse, and anxiety can significantly affect prognosis. Finally, the age, sex and health habits of the individuals involved also come into play in the analysis(21).

Association of depression with suicide-

Suicide is associated with the presence of depression. The feeling of hopelessness appears to be more important than other measures of severity in assessing the risk. Surprisingly, the risk is variable and not consistently substantially elevated in association with psychotic depression. Comorbid anxiety, substance abuse, and personality disorders are adverse prognostic indicators. The operative word for risk assessment is "early". The chances of suicide are increased, sooner after the diagnosis of depression, earlier in the life course of the illness, during the first few months after the initiation of therapy, earlier in the course of hospitalization and the first month or two after discharge from inpatient care(33).

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 overdosage hazards than the first- and second-generation antidepressants, their principal mechanism of action, neurotransmitter uptake inhibition, is certainly not a novel one (19). 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%) 6week placebo response rate, requiring large numbers of subjects (over 100) to demonstrate a

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 the U.S. versus European settings must also be taken into account in assessing response data. Also, 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 (20).

Another Treatment:- Mild depression can be effectively treated with either medication or psychotherapy. Moderate to severe depression may require an approach combining medication and psychotherapy32Drug Treatment: 50-65% of patients respond to the first antidepressant. No particular antidepressant agent is superior to another in efficacy or time to respond. Choice can be guided by matching patients' symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response. Relative costs can also be considered (e.g., generics). UMHS preferred agents are Fluoxetine (generic) and citalopram (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 was 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).

CONCLUSION

Adherence to antidepressant treatment is a major problem all over the world. Emphasizing the importance of a good use of antidepressant drug treatment is especially relevant for those patients more likely to follow it poorly, which would be those whose major psychiatric diagnosis is neither an effective nor an anxiety disorder, with a lower sociocultural level, low income, taking other drugs for concomitant organic diseases and/or living in rural areas with more difficult access to specialized care. In these patients, it is particularly important to insist on the relation between good treatment use and therapeutic response, with personalized information, and the nearest possible follow-up. Psychiatrists and general practitioners should inquire whether their patients adequately understand and follow instructions, and offer them the chance to work together to solve difficulties that may arise during antidepressant treatment. In the majority of the papers, the treatment is used properly in less than 40% of the patients, among different countries and cultures. In the group of better adherence are included patients diagnosed with affective disorders, more than with depressive or anxiety symptoms

not making up a major depressive disorder. When people are taking more drugs to treat somatic illnesses are less prone to follow antidepressant treatment properly. Treatment response is directly dependent on a correct psychopharmacological intake, so it's mandatory to reinforce it, to explain its action mechanisms properly, according to patients' sociocultural level, and to check it frequently, particularly if the response is not good. Physicians have to take into account the two components of adherence: persistence and compliance and question about them in all the visits. We will like to reinforce the importance to measure adherence and compliance, to prescribe an antidepressant that has minimum side effects, to inform properly of these effects and the response latency, and to reinforce all the problems that can be found with psychoeducation.

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