DEPRESSION: PREVALENCE, PATHOGENESIS AND TREATMENT OPTIONS

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ABSTRACT
Depression represents a major public health problem that is characterized by disturbance of mood, poor concentration, loss of sense of control and a subjective experience of great distress. It affects the thinking and functioning processes of an individual, greatly diminishes his or her social role and productivity, even leading to suicide. The incidence of depression is gradually on a rise and afflicts all socioeconomic levels. Prevalence studies give very high figures of depression in all parts of the world. The pathogenesis of this mental health problem is very complex. Genetic factors greatly contribute in etiology of depression and the heritability of this illness is greater in females. Abnormalities in membrane bound signal transduction systems and intracellular signaling systems play an important role in the etiology of depression. Deregulation of the hypothalamic-pituitary adrenal axis and altered levels of several brain neurotransmitters such as serotonin, norepinephrine, glutamate, gamma amino butyric acid and dopamine are also implicated in depression. The cause and effect relationship in this mental disorder still remains unclear. Therapies that are available to treat depression are limited and suboptimal with regard to their efficacy and tolerability. These therapies include pharmacotherapy, psychotherapy, exercise therapy, electro convulsive therapy, repetitive transcranial magnetic stimulation, phytotherapy, meditation, phototherapy and negative ion therapy.

INTRODUCTION
Depression is a common mental health problem, seen frequently in general medical settings (Katon and Schulberg, 1992). It constitutes a substantial proportion of the global burden of disease and is one of the major causes of disability and premature death (Licinio and Wong, 1999). The symptoms of depression, such as poor concentration, low mood and lack of interest or pleasure effect the patient’s capabilities for work and logical communication and leading to suicide (Johnson et al., 1992). Major Depressive Disorder (MDD) was identified by the World Health Organization in 2001 as the fourth leading cause of disability and premature death in the world. It is estimated that by the year 2020 MDD would be second to ischemic heart disease in regard to disease burden (Schutter and Honk, 2005). Depression ranges from a milder condition bordering normal condition to severe depression accompanied by hallucinations and delusions.

Depression is an exceptionally disabling condition and the disability is often not widely acknowledged, in part, because of the stigma associated with this illness. The negative attitudes of depression can impair judgment and reduce problem-solving abilities. It is perhaps this latter aspect of depression that is especially worrying in relation to socio-economic inequalities. In addition to disability, there is evidence that depression can also lead to increased mortality (Eddleston et al., 1998).
There is growing concern over the rising rates of suicide due to depression in many developing countries, particularly among adolescents and young adults (Eddleston et al., 1998). The suicide rate in depressed persons is 8 times higher than that of general population (Monk, 1987). Deliberate self-harm which does not lead to death is far more common than complete suicide and is becoming the commonest reason for emergency medical treatment in some developing countries (Eddleston et al., 1998).

Prevalence of Depression

The symptoms of depression are common and reported in all populations of the world (Ustun and Sartorius, 1995). The World Health Organization media center published a fact sheet in 2001 on mental and neurological disorders which stated that 25% of individuals develop one or more mental or behavioral disorders at some stage in their lives, in both developed and developing countries (WHO, 2001). One other study concluded that 13% to 20% of the population has some depressive symptoms at any given time and about 5% of the population is assumed to suffer from major depression (Licinio and Wong, 1999).

Depression in young people often co-occurs with other mental disorders, most commonly anxiety, disruptive behavior, or substance abuse disorders (Weissman et al., 1999). In Pakistan, the adjusted prevalence of depressive disorders is 44.4% (Husain et al., 2000). Ilyas et al. (2004) reported that mean prevalence of depressive disorders and anxiety in Pakistan is 34%.

Diagnosis of depression

According to the Diagnostic and Statistical Manual of Mental Disorder IV, if five or more than five of the following symptoms are present in any person for more than two weeks than s/he will be considered depressed (Liebowitz et al., 1994). The symptoms are sad (low mood, irritable), marked diminished interest or pleasure in almost all activities, significant weight loss or weight gain, insomnia or hypersomnia, observable psychomotor agitation or retardation, fatigue or loss of energy, feeling of worthlessness or inappropriate guilt, diminished ability to think or concentrate, recurrent thoughts of death or recurrent suicidal ideation, poor appetite or overeating and indecisiveness.

Pathogenesis of depression

The etiology of depression is still not well understood, despite extensive research. Many cases of depression are triggered by stressful life events. The intensity and duration of these events, as well as individual’s genetic endowment and social support network contribute to the likelihood of depression. The common predisposition to depression includes genetic, biological and psychosocial factors such as cognition and personality (Sadock and Sadock, 2003).

Studies of the genetics of depression have suggested that genetic factors account for approximately 40% of the variance in both males and females, with most of remainder being attributed to an individual’s unique environment (Thapar and McGuffin, 1996). More recently Kendler et al. (2001) have included male-female dizygotic, same sex monozygotic and dizygotic twins. They postulated that if broad definitions of illness are used, then the heritability of depression is approximately 1.4 times greater in women than in men. They further concluded that genes are correlated, and the impact of some loci on the risk for major depression may not be same for men and women. It seems likely that there are number of distinct genetic pathways to depressive illness. The 5-hydroxy tryptamine transporter gene on chromosome 17 is one of these, and it has been argued that an interaction with stressful life events appear to determine the liability to depressive illness (Caspi et al., 2003). On the other hand, Staley et al. (2006) argued that the decrease in 5-hydroxy tryptamine transporter gene availability in the diencephalon is pronounced in depressed women than in depressed men, thereby supporting higher incidence of depressive illness in females.
Neurochemical systems including membrane bound signal transduction systems and intracellular signaling systems that modulate gene transcription and protein synthesis, play an important role in the etiology of depression (Kalia, 2005). Intracellular signal transduction pathways are uniquely responsible for coordinating the cellular response. It follows that abnormalities in these pathways may lead to functional imbalance in multiple neurotransmitter pathways, which could account for the diverse clinical features. These may lead to bipolar disorders, such as mood fluctuations, psychotic features, neurovegetative symptoms and cognitive impairment (Ross, 1989). The complexity and diversity of signal transduction pathways continue to emerge.

Extensive literature search revealed that the activity of cAMP is very important in depression. cAMP regulates many cellular functions, such as metabolism and gene transcription (Scott, 1991). The major target for cAMP is another enzyme, cAMP-dependent protein kinase. This enzyme activity is a critical step in linking short-term changes in neurotransmitter signaling to lasting neurobiological changes (Scott, 1991). Several studies have reported that basal and receptor-activated adenylate cyclase activities are increased in patients with bipolar disorders. These changes may be linked to disturbances in the G-protein α sub units (Young et al., 1993). It has also been reported that bipolar patients have a significant increase in the cAMP-stimulated protein kinase activity as compared to controls and the mechanism(s) underlying the alterations of protein kinase and whether they reflect a primary condition or a secondary response to neurohormonal perturbations still remain unclear (Tardito et al., 2003).

Moreover, deregulation of the hypothalamic-pituitary-adrenal axis is also found in depressed persons (Thase and Howland, 1995). Corticotropin-releasing factor (CRF) is the principal neuropeptide involved in regulating the stress response. It is capable of reproducing the hormonal changes that are characteristically seen in depressed patients (Mitchell, 1998). Considerable evidences exist from cerebrospinal fluid studies, postmortem tissue receptor measurements and corticotropin releasing factor stimulation test studies to support the hypothesis that corticotropin releasing factor is hypersecreted in depressed persons that ultimately leads to hypercortisolemia. Under stressful conditions, the inhibitory effect of cortisol on adrenocorticotrophic hormone (ACTH) secretion is insufficient to counteract the extraneural input to the neuroendocrine cells secreting corticotropin releasing factor, consequently plasma ACTH levels are also increased. This hypothalamic pituitary-adrenal axis hyperactivity may be one of the contributors in the development of signs and symptoms of depression (Nameroff, 1992).

Several brain neurotransmitter systems such as glutamate, gamma amino butyric acid (GABA), serotonin, norepinephrine and dopamine have been implicated in depression (Kalia, 2005). Literature provides an evidence of abnormally low concentration of GABA in the occipital cortex of depressed patient as compared to healthy subjects (Sanacora et al., 1999). Intravenous administration of the selective serotonin reuptake inhibitor (SSRI) citalopram increases total occipital GABA levels in healthy volunteers (Bhagwagar et al., 2004). Thus suggest of that decreased level of GABA may be involved in the etiology of depression. One other study suggested a possible role of altered glutamatergic neurotransmission within the anterior cingulate cortex in the pathogenesis of depression and reported low glutamate concentration in the depressed patients (Auer et al., 2000).

The molecular mechanism by which this low concentration of GABA in the occipital cortex and altered glutamatergic neurotransmission within the anterior cingulate cortex causes the depression is still unclear.

The involvement of biogenic amines primarily norepinephrine and serotonin in depressive disorders was suggested by the
Depression: Prevalence, Pathogenesis and Treatment Options

finding many years ago (Agurell, 1981) and now their role in mental illness including depression is well recognized (Elhwuegi, 2004). Experimental and clinical evidences support the fundamental role of serotonin and norepinephrine, as well as the interactions between these systems in the etiology of depression. Substantial evidences have occurred, including changes in neurotransmitters and neurotransmitter metabolite concentrations, reuptake sites and receptors, to support the hypothesis that alteration in neuronal serotonergic and noradrenergic function occurs in the central nervous systems of patients with major depression (Nemeroff, 2002). Noradrenergic and serotonergic both systems are involved in antidepressant action, but the specific impairment that underlies depression is unclear and is likely to vary among patients. Antidepressant drugs activate norepinephrine and serotonin receptor mediated signal transduction cascades, involving protein kinase A and protein kinase C (Shelton, 2000). These kinases phosphorylate cAMP response element binding protein (CREB), which, in turn, enhances the gene expression, by binding to cAMP response elements (CREs) in the promotors of certain genes for the protein synthesis. Results from neurotransmitter depletion studies in depressed patients who have responded to treatment suggest that, while interaction between norepinephrine and serotonin are likely but neither of these two neurotransmitter systems is the final common pathway for the therapeutic effect of antidepressant drugs (Delgado and Moreno, 2000). The cause of depression is more complex than just an alteration in the levels of serotonin or norepinephrine (Delgado and Moreno, 2000). Although conclusive results have not yet been observed, compelling evidence from diverse independent research studies suggest that altered second messenger systems (Bezchlibnyk and Young, 2002) and abnormalities in monoaminergic neurotransmission play an important role based upon the efficacy of drugs that modulate these neurotransmitter systems (Schutter and Honk, 2005).

Currently, research focuses on how the biological abnormalities interrelate and how they correlate with behavioral and emotional patterns that seem to distinguish one subcategory of depression from another, and how they respond to diverse forms of therapy.

Treatment modalities

Course and treatment of major depression are among the most pressing public health concerns in medicine. It is therefore satisfying to observe that critical advances have been made in our fundamental understanding of this illness and related conditions in the past several years. Among the areas of major change have been advances in disease classification, an improved understanding of risk factors for the development of major depression, advances in the standards of clinical practice, enhanced societal acceptance of patients with the disease and their treatment and a substantial increase in our understanding of the underlying neurobiology of this common, disabling, and potentially lethal illness (Demitrack, 2005).

An individual’s genetic makeup strongly influences not only their likelihood of developing depression, but also whether or not they will respond well to a particular antidepressant treatment. Identifying those genes regulating susceptibility to depression will increase our understanding of disease pathophysiology and direct the development of treatments that correct underlying neurobiological pathology related to stress-related psychiatric illnesses (Crowley and Lucki, 2005).

The therapies applied to treat depression either individually or in combination include pharmacotherapy, psychotherapy, exercise therapy, electro-convulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), phytotherapy, meditation, phototherapy and negative ion therapy.

1) Pharmacotherapy

In 2003, available pharmacotherapy for depression was based almost entirely on
observations from the 1950s and 1960s. Agents that enhance monoamine transmitter function at their specific receptors are effective antidepressants (Owens, 2004). The drugs commonly used for the treatment of depression are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs) (Harvey and Champe, 2006) as mentioned in table 1.

The above drugs either increase the availability of monoamines, norepinephrine and 5-hydroxy tryptamine at their receptors in case of monoamine oxidase inhibitors (MAOIs) and or prevent their reuptake, as in case of tricyclic antidepressants, selective inhibitors of 5-hydroxy tryptamine reuptake and serotonin norepinephrine reuptake inhibitors (SNRIs) (Blier et al., 1987 and Murphy et al., 1984). Monoamine oxidase causes oxidative deamination of biological amines and regulates the intracellular concentration of catecholamine and 5-hydroxy tryptamine in the brain and the peripheral tissues (Yu et al., 1992).

2) Psychotherapy

It is one of the important therapies applied to treat depression. It offers people the opportunity to identify the factors that contribute to their depression and to deal effectively with the psychological, behavioral, interpersonal and situational causes. It involves verbal and nonverbal communication with the psychotherapist about thoughts, feelings, emotions and behaviors in individual, group or family sessions in order to change unhealthy patterns of coping in stressful conditions, encourage personality growth and improved interpersonal relations (Sadock and Sadock, 2003). Psychotherapy can be a very useful way in resolving emotional and interpersonal problems but it does requires a commitment of time and cooperation of individual(s). There are a wide number of different types of effective psychotherapeutic approaches utilized for the treatment of depression today that includes cognitive behavioral therapy, interpersonal therapy, rational emotive behavior therapy and family therapy (Sadock and Sadock, 2003).

3) Exercise therapy

Aerobic exercise is advised for the treatment of a wide range of medical disorders, including cardiovascular diseases, hyperlipidemia, osteo-arthritis, and diabetes etc. In addition, exercise may have a number of psychological benefits (Plante and Rodin, 1981) and it has been suggested as a potential treatment for a variety of psychiatric conditions, especially depression (Gullette and Blumenthal, 1996).

Epidemiological studies have reported that physical activity is inversely related to depressive symptoms (Stephen, 1998) and the gradual increase in the physical activity decreases the risk for depression (Camacho et al., 1991). A modest exercise such as brisk walking, jogging and cycling, three times per week for a period of 30 minutes is an effective treatment for patients with major depression (Babyak, 2000).

4) Electroconvulsive therapy (ECT)

Electroconvulsive therapy is the fastest way to relieve symptoms in severely depressed patients. ECT is generally used as a last resort when severe depression is unresponsive to other forms of therapy, or when these patients show a severe threat to themselves or others. It is believed that ECT works by using an electrical shock to cause seizures, leading to the release of many neurotransmitters at different sites in the brain, which are responsible to relieve the symptoms of depression. Literature suggests that ECT is a valid therapeutic tool for treatment of depression, including severe and resistant forms (Pagnin, 2004).

5) Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation (TMS) has been recently accepted as a treatment for patients with major depression (Fujita, 2005). It enhances cortical excitability, which shows
antidepressant effect when applied over the left prefrontal cortex (Schutter and Honk, 2005). In rTMS, stimuli are applied to the same brain area repeatedly for several consecutive seconds. This treatment alters the biochemistry and firing patterns of neurons in the brain. Preliminary research indicates that rTMS exerts changes in receptor binding generally similar to that of antidepressant action (Ben-shachar Ct al., 1999) and also alters the level of several neurotransmitters including dopamine and serotonin at the specific sites in the brain (Ben-shachar et al., 1997). Fujiki and Steward (1997) reported that rTMS modulates the expression of c-fos mRNA gene in the paraventricular nucleus of thalamus and in the frontal and cingulate cortices that are important for cellular signaling and could play a role in alleviating depression.

6) Phytotherapy

The use of natural medicines including plants to control diseases is a centuries old practice, based on the experience of many generations of traditional healers and herbal practitioners. Greeko-Arabic (Tibb), Ayurvedic (Indian), Traditional Chinese Medicine (TCM) and other herbal medical practices have claimed for centuries that extract from plants can be effectively used for the alleviation of different types of ailments including neurological diseases.

Herbs have played significant role in the management of neuropsychiatric disorders. There are many plants, which are used traditionally for the treatment of depression. Few to mention viz Curcuma longa (Yu et al., 2002), Rhazya stricta decne (Au et al., 1998), Banxia Houpu decoction (Luo et al., 2000), Bacopa monniera (Sairam et al., 2002), Apocynum venetum (Butterweck et al., 2001) and Morinda officinalis (Zhang et al., 2002) etc. The antidepressant activity of these above mentioned plants has been scientifically validated by different experiments. The standardized extract of Hypericum perforatum (St. John’s wort) is the most promising herbal antidepressant which is used as a therapeutic agent for the depression in Europe and many other countries and it extends well beyond the traditional field of herbal medicine (Muller, 2003). It has been shown to alleviate

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<tr>
<th>Class</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Monoamine oxidase inhibitors (MAOIs)</td>
<td>Phenelzine, Tranylcypromine</td>
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<td>MAO-A inhibitor (Selective)</td>
<td>Moclobemide</td>
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<tr>
<td>Tricyclic antidepressants (TCAs)</td>
<td>Amitriptyline, Clomiprine, Desipramine, Protriptyline, Citalopram, Escitalopram, Fluvoxamine,</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Fluoxetine, Paroxetine, Sertaline</td>
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<tr>
<td>Serotonin Norepinephrine reuptake inhibitors (SNRIs)</td>
<td>Duloxetine, Venlafaxine</td>
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<tr>
<td>Atypical antidepressants</td>
<td>Bupropion, Mirtazapine, Nefazodone, Trazodone,</td>
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symptoms of mild to moderate depression, and seems to offer significant advantages over conventional antidepressants (Di Carlo et al., 2001).

7) Meditation
Meditation is an ancient technique with many modern variations and is getting popular now-a-days. It is a self-regulation of attention to suspend the normal stream of consciousness. A goal of meditation is to reach a state of thoughtless awareness, during which a person is passively aware of sensations at the present moment. It is an innovative, empirically validated treatment to prevent relapse in people who have recovered from depression (Mason and Hargreaves, 2001). It is also beneficial to patients with active depression and anxiety (Finucance and Mercer, 2006).

8) Phototherapy
Phototherapy is also one of the nonpharmacological modalities recommended to treat seasonal affective disorder (SAD) or depression. It is more popular in Scandinavian countries. Bright light presents a promising treatment for SAD, but it took at least 3 weeks for a significant effect to develop (Charmane et al., 1998). It appears to act as a specific antidepressant in patients with SAD. Clinical improvement is further enhanced by its use in combination, or as adjuvant to medication (Michael et al., 1998).

9) Negative ion therapy
Negative ions are atoms or molecules of oxygen in the air that are produced naturally by the lighting, wind and water falls etc. Negative air ionizers are electrical devices that produce negative air ions and are used in the treatment of seasonal winter depression. It acts as specific antidepressants in patients with seasonal affective disorder (Michael et al., 1998) that makes it useful as an alternative or complimentary to light therapy and medications (Terman and Terman, 1995).

REFERENCES


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