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PATHOPHYSIOLOGY AND HERBAL DRUG TREATMENT OF ANXIETY

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ABSTRACT

Anxiety is CNS psychological disorder which is due to various reasons like fear; threaten of future, stress etc. The symptoms of anxiety are shivering, cold hands, nausea, vomiting, headache etc. There are five types of anxiety: GAD (Generalised Anxiety Disorder), Panic disorder, PTSD (Post traumatic stress disorder), SAD (Social Anxiety Disorder), OCD (Obsessive Compulsive Disorder). Main neurotransmitter's (norepinephrine, serotonin, and GABA) which are involved in the pathophysiology of anxiety, and it is the main reason of causing anxiety. Norepinephrine is associated with the autonomic nervous system with cardiac diseases: over activity of Norepinephrine down regulates the α-2adrenoreceptors which causes the GAD type of anxiety disorder, Serotonin reuptake transporter site, or effect of 5-HT at the postsynaptic receptors (e.g., 5- HT1A, 5-HT2A, and 5-HT2C) may play a role in anxiety disorders and GABA is inhibitory neurotransmitter which has $GABA_A$ and $GABA_B$ receptors present in the brain. The low level of GABA in people is also being the cause anxiety. Receptors present in the brain which are also responsible of anxiety are: BZD, Dopamine, GABA, histaminic, adenosine receptors, serotonin, adrenergic, opioid receptors etc. Allopathic medicines of anxiety have many side effects as the cause sedation, hallucinations, and dependence to overcome these problems herbal medicines are used in the treatment of anxiety as they have lesser or no side effects. Nowadays, herbal drugs are mostly preferred because population is more aware and rely on the use of traditional medicine. Some of the herbal drugs are valerian, neem, chamomile, *Zinziber officinale*, rosemary, lavender, *Angelica sinensis* etc.

ANXIETY:

The anxiety is derived from Latin **"anxietas"** which means choke, throttle, trouble and upset. Anxiety is psychological CNS disorder and most common form of CNS disorder in the world. It is the unpleasant state of inner commotion, followed by the nervous behaviour characterised by rumination, worrying, uneasiness, apprehension, and fear about future uncertainties which are depend upon the real or imaginary things which may affect the physical and psychological health. Common or situational anxiety is a normal response to stressful situation though symptoms can be severe; they are temporary or usually last no more than 2 or 3 weeks[6].

For more than 2500 years, physicians have distinguished the clinical conditions which we call affective or anxiety disorder from such everyday feelings as fear, restlessness, and despondency, feelings which overwhelm each of us, at one time or another**.** From the time of Hippocrates up until well into the 17th century, the description and interpretation of anxiety and depression were dominated by the doctrine of bodily fluids (humores). And, until quite recently, all manner of ideas involving neural energy overshadowed discussions of phenomena such as neurasthenia, inhibition, and motor agitation.

Prior to about 1850, anxiety was not considered to be a distinct form of psychopathology in the medical literature. This is of particular importance to the recent debate on the demarcation between affective and anxiety disorders. For hundreds of years, the symptoms of anxiety had simply been seen as part of melancholia. In the course of the past century and the present one, the various forms of anxiety came to be distinguished from depressive disorders, on a variety of grounds. In the light of the century-old merging of anxiety and depression, a reconsideration of these grounds is therefore a matter of considerable topical interest. The frequent occurrence of anxiety with psychotic symptoms did not, of course, go unnoticed by 19th century psychiatry. Wernicke, however, was the first to use the term anxiety psychosis. In Wernicke's opinion, frightening cognitions, hallucinations, delusions and delusory ideas were the result, rather than the cause, of the emotion of anxiety. He explained the psychotic phenomena seen in anxiety psychosis by the intensity of the anxiety itself. The history of the classification of anxiety disorders since the time of Beard can be seen as a peeling-away of layers of the concept of neurasthenia. The anxiety attacks experienced by many neurasthenia sufferers were not accompanied by any subjective feeling of anxiety[5].

Anxiety includes the effects such as heart palpitations, fatigue, nausea, chest pain, shortness of breath, stomach aches, or headaches. Blood pressure and heart rate are increased, sweating

is increased, and blood flow to the major muscle groups is increased. Immune and digestive system functions are inhibited. External signs of anxiety may include pale skin, sweating, trembling, and papillary dilation[2].

Some of the behavioural symptoms of anxiety include: As in the case of depression, people who suffer from anxiety will tends to: Avoidance of performance, Avoidance of the feared thing, Drink excessively, Excessive attention to control or details in order to prevent mistakes, Indulge in promiscuity or reckless sex, Other reckless behaviours such as excessive spending, Social avoidance. Some people will avoid responsibility in order to decrease their anxiety[1].

SYMPTOMS OF ANXIETY:

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There are many emotional symptoms involved as dread, jumpy, anticipating the worst, irritability, restlessness, watching (and waiting) for signs (and occurrences) or danger. Mental symptoms of anxiety such as confusion, hyper reactivity, hyper sensitivity, hyper vigilance, poor concentration, poor judgment and poor memory[4].

TYPES OF ANXIETY:

Anxiety is divided into five categories:

1. Panic disorder.
2. Generalised anxiety disorder.
3. Social anxiety disorder.
4. Obsessive compulsive disorder.
5. Post-traumatic stress disorder.

1. PANIC DISORDER:

Panic disorders are defined as the occurrence of panic attacks repeatedly and are unexpected. So, the panic attack and panic disorder are differentiated terms. Panic attacks are defined as discrete periods of sudden symptom onset usually peaking in 10 minutes and usually last no more than 20 to 30 minutes and it can occur with most anxiety disorders[6].

SYMPTOMS OF PANIC DISORDER:

1. Sweating
2. Trembling
3. Nausea
4. Shortness of breadth
5. Chest pain
6. Fear of dying
7. Going crazy

2. OBSESSIVE COMPULSIVE DISORDER:

Obsessive compulsive disorder is an unrealistic state of anxiety where the person or patient is worried about 2 or more life circumstances about to six or more months. An obsession which is experienced as non meaningful and inappropriate skittish thought, impulse, or image which cause discernible anxiety. A compulsion is defined as behaviour of repetition or mental act. Generally compulsion is featured in respond to an obsession. Diagnostically, compulsive behaviour is not pleasurable and is designed to prevent discomfort or the occurrence of a dreaded event that is often unknown. For example, many patients are obsessed with feelings of doubt (e.g., whether a door was left unlocked), causing them marked distress, and leading to repetitive checking (or compulsive behaviours)[6].

The most common Compulsions are:

1. Washing and cleaning,
2. Checking,
3. Requesting
4. Demanding assurances.

The most common Obsessions are:

1. Concern with germs or dirt
2. Repeated doubts
3. Need to have things in a particular order.

3. POST TRAUMATIC STRESS DISORDER:

PTSD is commenced when the person go through any physical harm or having the threat of physical harm. PTSD is the result of many traumatic incidents, such as depredation, rape, torture, being kidnapped, child abuse, car accidents, train wrecks, plane crashes, bombings, or natural disasters such as floods or earthquakes. Symptoms may be lasts for few weeks, or upto many stay for many years. People with PTSD may startle easily, become emotionally numb, lose interest in things they used to enjoy, have trouble feeling affectionate, be irritable, become more aggressive, or even become violent.

4. GENERALISED ANXIETY DISORDER (GAD):

Generalised anxiety disorder is an unrealistic state in which the person worries about two or more life circumstances which lasts for 6 months or more years. Patients suffering from GAD can't seem to get rid of their concerns, even though they usually know that their anxiety is getting more worsen than the situation warrants, even though they can't relaxing and having difficulty in concentrating. Often they have trouble falling asleep or staying asleep.

SYMPTOMS OF GAD:

1. Muscle tension
2. Clammy hands
3. Dry mouth
4. Nausea
5. Sweating
6. Diarrhoea
7. Urinary frequency

5. SOCIAL ANXIETY DISORDER (SAD):

It is diagnosed when people become overwhelmingly anxious and excessively self conscious in everyday social situations. People with social phobia have an intense, persistent, and chronic fear of being watched and judged by others and of doing things that will embarrass them. They can worry for days or weeks before a dreaded situation. This fear may become so severe that it interferes with work, school, and other ordinary activities, and can make it hard to make and keep friends.

While many people with social phobia realize that their fears about being with people are excessive or unreasonable, they are unable to overcome them[6].

SYMPTOMS OF SAD:

1. Blushing

2. Sweating
3. GI discomfort
4. Tremors
5. Palpitations
6. Avoidance
7. Embarrassment

MECHANISMS INVOLVED IN THE ANXIETY:

MECHANISM OF ANXIETY [3]

- Over activation of brain neurotransmissions and neuronal firing.
- Under inhibition of brain neurotransmissions and neuronal firing.
- BOTH.

MECHANISM-OVERACTIVE NEURONS

Anxiety is related to excess

- Stimulatory neurotransmitter (glutamate)
- Calcium influx, pre or post-synaptic.

NEURONAL EXCITATION (ROLE OF GLUTAMATE)

- Excitatory amino acid neurotransmitter
- Mediates excitatory neurotransmission
- Interacts with most synapse.
- Stress activates cortical and limbic glutamate neurotransmission.
- Increased neurotransmission is through NMDA (N-Methyl D-Aspartate) receptors.

MECHANISM-UNDERACTIVE NEURONS: Anxiety is related to insufficient

- Inhibitory neurotransmitters (GABA) Gamma Amino Butyric Acid
- $GABA_A$ receptor function.
- Enhancement of GABA.

PATHOPHYSIOLOGY OF ANXIETY DISORDER:

Behavioural traits of anxiety disorders are passed from parents to child, which tends to run through family structures. Studies comparing the risk of psychiatric illness in identical twins (who share 100% of their DNA) have found that, if one identical twin has a psychiatric condition, then the other twin will have the same condition which is approximately 50%. Non genetic factors, including environmental influences occurring throughout the lifespan, must also contribute to the risk of developing an anxiety disorder. The human body attempts to

maintain homeostasis. Anything in the environment that disturbs homeostasis is defined as a stressor. Homeostatic balance is then re-established by physiologic adaptations that occur in response to the stress. The stress response in humans involves a cascade of hormonal events, including the release of corticotrophin releasing factor (CRF), which, stimulates the release of corticotrophin, leading to release of the stress hormones (glucocorticoids and epinephrine) from the adrenal cortex. The glucocorticoids typically exert negative feedback to the hypothalamus, thus decreasing the release of CRF6. The stress response is hardwired into the brain of the typical mammal and is most often triggered when survival of the organism is threatened. The primate stress response can be triggered not only by a physical challenge, but also by the anticipation of a homeostatic challenge. As a result, when humans chronically believe that a homeostatic challenge is about to occur, they enter the realm of neurosis, anxiety, and paranoia. The amygdala is the primary modulator of the response to fear/ anxiety inducing stimuli. It is registering the emotional significance of stressful stimuli and creating emotional memories. The amygdala receives input from neurons in the cortex. Being stuck in traffic, crowded shopping mall, or on an airplane that may serve to trigger the anxiety response in a susceptible individual via this mechanism. The amygdala also receives sensory input that bypasses the cortex and tends to be subconscious. An example is that of a victim of sexual abuse who suddenly finds herself acutely anxious when interacting with a number of friendly people[3]. It may take her a few moments to realize that characteristics of the individuals with whom she is interacting remind her of the person who abused her. When activated, the amygdala stimulates regions of the midbrain and brain stem, causing autonomic hyperactivity, which can be correlated with the physical symptoms of anxiety. Thus, the stress response involves activation of the hypothalamic-pituitary-adrenal axis. This axis is hyper active in depression and in anxiety disorders.

NEUROTRANSMITTERS INVOLVED IN PATHOPHYSIOLOGY OF ANXIETY:

Neurotransmitters are chemicals located and released in the brain to allow an impulse from one nerve cell to pass to another nerve cell. There are approximately 50 neurotransmitters identified. Some common neurotransmitters are acetylcholine, nor epinephrine (NE), dopamine, serotonin and (GABA). Acetylcholine (Ach) and NE are excitatory neurotransmitters while dopamine, serotonin, and GABA are inhibitory. Each neurotransmitter can directly or indirectly influence neurons in a specific portion of the brain, thereby affecting behaviour[8-9].

SOME OF THE RECEPTORS IN THE BRAIN RESPONSIBLE FOR ANXIETY:

1. **Benzodiazepine receptors (BDZ-Rs)**[7]
2. **Serotonin receptors (5-hydroxytriptamine):**
   - **a)** 5-hydroxytryptamine$_{1A}$ (5 HT$_{1A}$)[11]
   - **b)** 5-HT$_3$ receptor: 5-HT$_3$ receptor antagonism contributes the anxiolytic effect[10]
   - **c)** Selective 5-HT reuptake inhibitors (SSRIs).
3. **$_{\gamma}$-amino butyric acid receptor (GABA)**[12-13-14]
4. **GABA$_A$- benzodiazepine receptor**
5. **Histamine receptor (H-receptor)** Histamine receptor plays an important role in anxiety and other CNS disorders with reference toH_1, H_2, H_3receptors[15]
6. **Opioid receptors**[20]
7. **Adenosine $_{A1}$ receptors**[17]
8. **Dopaminergic receptor:** (D_2) receptors[16]
9. **Somodendriticauto receptors**[16-19]
10. **Adrenergic receptors**[18]

Some Brand Drugs used in Anxiety: ENXOLAM, ALPRAX, ALPRAX SR, ANXIT, ANXYL, ANAX, ZOLAX, BUSPIN, EQUILLIBRIUM and LIBRIUM (chlordiazepoxide, common salt).

Side Effect of Allopathic Formulations/Anxiolytics: Anxiolytic substances, mostly belonging to the BZ group, occupy a prominent post in the ranking of the most utilized[24] to minimize stress, tension and anxiety[23]. As a result of these effects, benzodiazepines are also able to treat insomnia[25-26]. However, the anxiolytic drugs have an unfavourable risk/ benefit ratio, as they produce anterograde amnesia, dependence, abstinence syndrome, paradoxical reaction in humans and decay of psychomotor functions[21-22.] These symptoms can lead to an increased possibility of car accidents and of fractures. Therefore, research has been conducted to identify safer, more specific medications possessing anxiolytic effect without the complications. In past few years, several herbal medicines have been used for the management of anxiety.

HERBAL DRUGS USED IN THE TREATMENT OF ANXIETY DISORDER:

Plants that possess the therapeutic value or exert beneficial pharmacological effects on the human body are called as herbal drugs. They synthesize and accumulate some secondary metabolites like alkaloids, glycosides, saponins, terpenoids, flavanoids, cyanogenins which possesses the medicinal value in the treatment of the various diseases and disorders like

cancer, CNS disorders, CVS disorders, liver disorders, etc. in past three decades, utilization and demand of medicinal plants increased globally. Due to this the international trades in medicinal market grow phenomenally, often to the detriment of the natural habitats and mother population in the countries of origin. Today's world's population is more aware and rely on the use of traditional medicine, which is predominantly based on plant material. The traditional medicine refers to a broad range of ancient natural health care practices and these medicinal practices have originated from time immemorial and developed gradually, to a large extent, by relying or based on practical experiences, without significant references to modern scientific principles[27]. The ethno pharmacology knowledge and experimental base allows drug research from 'Clinics to Laboratories'—a true Reverse Pharmacology Approach[26]. In this process, 'safety' remains the most important starting point and the efficacy becomes a matter of validation. A golden triangle consisting of Traditional Knowledge, Modern Medicine and Modern Science with systems orientation will converge to form an innovative discovery engine for newer, safer, affordable and effective therapies[28].

SOME HERBAL PLANTS USED IN ANXIETY ARE:

Valerian (*Valerian officinalis*)[29]:- *Valeriana officinalis* is a hardy perennial flowering plant. Valerian is native to Europe and Asia and has naturalized in eastern North America. Plant has been used as Carminative, insomnia, anxiety.

Chamomile (*Matricaria recutita*)[30]**:-** Chamomile plant contains chemical constituent i.e. apigenin. It is used in the treatment of anxiety. Allergic conjunctivitis, anaphylaxis are the side effects of *Matricaria recutita*. Plant is restricted in pregnancy and breast-feeding. And also it is teratogenic and abortifacient.

***Lavender officinalis* (lavender)**[33]**:-** Lavender is a flowering plant in the family Lamiaceae, native in northern Spain. It is a strongly aromatic shrub growing as high as 1 to 2 metre (3.3 to 6.6 ft) tall. The leaves are evergreen, 2–6 centimetre long, and 4–6 millimetre broad. Uses of lavender are CNS depression, anticonvulsant, sedative, restlessness, insomnia. Side effects of lavender are constipation, dermatitis, CNS and respiratory depression, headache, miosis, nausea, vomiting, headache.

Rosemary (*Rosmarinus officinalis*)[31]**:-** Rosemary is commonly known as rosemary, is a woody, perennial with fragrant, evergreen, needle-like leaves and white, pink, purple, or blue flowers, native to the Mediterranean region.

***Angelica sinesis* (olive) Diels**[32]**:-** It is native to Eastern and southern Asia. Single or repeated use (for 7 days) of male rats with aqueous extract 100mg/kg, 200mg/kg p.o reduced anxiety in Elevated plus maze(EPM). Anxiolytic effect is abolished by pindolol (10mg/kg,i.p.)

***Euphorbia hirta* Linn**[34]**:-** It is native to Asia and warmer region of the world. The extract shows anti-anxiety activity at 2g/kg, s.c. in vogel type anti-conflict method in mice. Adenosine produced anxiolytic behaviour at a dose of 30mg/kg by s.c.

***Magnolia dealbata* Zuce**[35]**:-** This is found in North America and Central America. The extract (30mg/kg, 100mg/kg, 300mg/kg) dose dependent decrease in anxiety when tested in Elevated plus maze and in exploratory behaviour in rats. The effect may be due to magnolol.

Neem *(Azadirechta indica)*[37]***:-*** This is a larger plant found everywhere in the India. Aqueous extract of Neem leaves (10-200mg/kg) produced anxiolytic effect in Elevated plus maze in rats. The extract has been found to contain margosine, margosic acid, margosopicrin as an active constituents.

Zingiber officiinale[36]**:-** Zinger is a creeping perennial on thick tuberous rhizome which spreads underground. In the first year a green, erect stem about 60cm high grows from this rhizome. Ginger is a rich source of volatile oil.Ginger contains zinzeberine, phelendrene and gingerol. Animals treated with Zinziber produced anxiolytic activity using Elevated plus maze.

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