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ADVANCEMENTS IN UNDERSTANDING AND TREATING ANXIETY DISORDER

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ABSTRACT

Anxiety is a typical human feeling that everyone occasionally feels. Anxiety may, nevertheless, be regarded as an anxiety disorder when it manifests itself excessively and interferes with daily life. A set of mental health illnesses known as anxiety disorders are characterised by extreme, ongoing worry or fear. Therapy and medication are frequently used in the treatment of anxiety disorders. Anxiety disorders are frequently treated using cognitive-behavioural therapy, which assists patients in recognising and altering harmful thought patterns and behaviours. To help alleviate symptoms, doctors may also prescribe drugs like benzodiazepines and selective serotonin reuptake inhibitors (SSRIs). In order to enhance outcomes and quality of life, it is crucial for people with anxiety disorders to get professional assistance as soon as possible. A good diet and regular exercise can also help manage the symptoms of anxiety disorders. Stress management practises can also be useful.

Keywords: Panic disorder, Generalised anxiety disorder, Specific phobia, GABA, Benzodiazepines

INTRODUCTION:

The most common central nervous system disorder is anxiety. "It is characterised as an uncomfortable emotional state accompanied by restlessness, distress, and worry or fear around certain known or unknown potential harm." One-eighth of the population suffers from anxiety, which has been a crucial topic of research in psychopharmacology during the past ten years. Anxiety is the most widespread mental ailment **[1]**. Nails licking, twitching fingertips, heart palpitations, sleeplessness, shyness, bad

dreams, pressures or discomfort, breathing difficulty when one is not working hard, and dizziness are some of the symptoms of anxiety. Other symptoms include feeling of insecurity and helplessness that is frequently without a concrete cause, a communication barrier, a mental and emotional weird obsession, and disruptions to one's ability to think clearly and concentrate **[2]**. Around 15-20% patients in general practice are'present with anxiety disorders. It is characterized by excessive rumination, worrying, uneasiness, apprehension and fear about future uncertainties either based on real or imagined events, which may affect both physical and psychological health. Recent surveys have found that as many as 18% of Americans, 20.7% of Indians and 14% of Europeans may be affected by one or more of them. Almost one-quarter of all individuals will experience an anxiety disorder at some stage in one 's life. The prevalence of mood disorders is 19.2% in men and 30.5% in women. Anxiety disorders are extremely common in adolescents and young adults. Anxiety disorders were discovered in 15.4% of 7 to 11-year-old children. According to one survey, only about 14% of people with such psychiatric issues receive treatment. Anxiety can exacerbate a number of physical and mental illnesses, as well as make recovery from other problems more difficult **[3]**.

TYPES OF MOOD DISORDERS

- Generalized anxiety disorder
- Social anxiety disorder
- Panic disorder
- Phobias

Panic disorders:

Those who have panic disorder frequently experience unplanned anxiety attacks. Even if there's no immediate threat or trigger, anxiety attacks are brief episodes of acute death, uneasiness, or a sensation of losing control. Panic disorder does not always follow a panic attack. A panic attack can cause the following symptoms: Heart problems, racing heart, flushing, shivering, or tingling, feelings of impending disaster, and a feeling of being out of control **[4]**.

Disorder of Generalized Anxiety:

A persistent worry or anxiety that could hinder everyday activities is a defining feature of Generalized anxiety disorder(GAD). It differs from experiencing occasional concern or anxiety as a result of stressful life circumstances. People with GAD experience chronic anxiety for months or even years **[5]**. Anxiety, tenseness, or restlessness, having difficulties focusing, becoming tired easily, being angry, getting headaches, muscular pains, stomach pains, or other unexplainable ailments, struggling to control stress-related thoughts, and having difficulty or staying asleep are the

common symptoms of generalized anxiety **[6]**.

Disorders associated to phobias:

Phobias are defined as an intense aversion to or dread of specific things or situations. Although while it can be acceptable to feel anxious in some circumstances, the dread that people with phobias experience is disproportionate relative to the added risk that the situation or object poses **[7]**.

Agoraphobia Individuals with phobias are dreadfully scared of at least two of the following situations: Using public transportation, moving through open or enclosed spaces, and standing in a crowd are all examples of stressful travel situations. People with agoraphobia frequently steer clear of these situations because they think it will be challenging or impossible to leave if they suffer severe anxiety or other painful symptoms **[8]**.

Particular phobia As the name suggests, those who have a specific phobia experience excessive fear in regard to a particular group of objects or situations. Here are a few instances of particular phobias: Height, particular creatures, like dogs, snakes, or spiders, self-injecting **[9]**.

Social Anxiety Disorder: A persistent worry of being viewed and judged by others is a defining feature of social anxiety disorder. The fear of social circumstances can be so intense for some persons with a condition called social anxiety that it seems to be without their control. Some individuals may suffer fear that keeps them from attending work or school or carrying out regular duties. A pounding heart, flushing, perspiring or trembling are all symptoms of social anxiety disorder **[10]**.

SYMPTOMS

Excessive heart rate, Rapid breathing, Hyperventilation, Sweating, Fluttering, Tiredness Difficulty focusing or thinking about anything other than the current stress, Insomnia, Gastrointestinal problems, Difficulty managing the stress **[11]**.

CAUSES

Genetics: Anxiety disorders may be passed down through families to future generations. anxiety disorders may be caused by dysfunctional fear and emotion-controlling brain circuits, according to some research. Environmental stress is a result of traumatic events you have either experienced or watched. Anxiety disorders are usually associated with adverse life events such a loved one's death, being attacked or witnessing violence, and others. Withdrawal or abuse of drugs: Some medications may be used to mask or alleviate the symptoms of anxiety. Anxiety disorders and alcohol and drug abuse can coexist. Health problems: Certain thyroid, heart, and lung conditions might worsen or produce symptoms that are reminiscent of anxiety disorders **[12]**.

EPIDEMIOLOGY

Mood disorders are the most prevalent mental disorders in the community, and epidemiological studies show that they are exceedingly prevalent and a significant cause of functional disability. Phobias are the most prevalent, with simple phobia and agoraphobia being the most prevalent types. post-traumatic stress disorder are less prevalent and there are conflicting findings for social phobia (SP) (2 % to 16 %) and GAD (3 %-30 %). These studies emphasise how important it is to characterise illnesses precisely by utilising precise diagnostic and assessment criteria **[13]**. Panic attacks are more common in people who are separate, divorced, or bereaved; their frequency is highest in people between the age of 25 and 44 and lower in people over 65. Phobia disorders first occur in early childhood, whereas post-traumatic stress disorder (PD) first appears in early adulthood. Clinical research has prioritised risk factors such as life events, childhood experiences, and familial characteristics over epidemiological research. Chronic and persistent, anxiety disorders typically co-occur with substance addiction, depressive disorders, and other anxiety disorders. Depressive disorders or substance abuse are more likely to occur later than anxiety disorders. Risk factors including functional impairment and quality of life might be impacted by comorbid disorders **[14]**.

ETIOLOGY:

There is evidence that a combination of multidimensional variables contributes to anxiety disorders. Clinically significant syndromes develop when a person's genetic predisposition combines with stressful or traumatic circumstances **[15]**. Conditions like the ones listed below can make anxiety worse: Medical supplies, Natural remedies, Abuse of drugs, Childhood trauma and memories, Stress, physical illnesses like diabetic or other co-morbidities like depressive episodes, heredity, 1st degree relatives with GAD (25%), contextual variables including child maltreatment, and substance addiction are only a few of the causes of anxiety. The proportional weight of these elements will probably vary because there are so many distinct anxiety illnesses. Although while specific genes are lacking, some anxiety illnesses, like panic disorder, seem to have a stronger genetic base than others. A stressful life event is more frequently linked to other anxiety disorders. Interventions **[16]**.

PATHOGENESIS OF ANXIETY DISORDER

The mediators of anxiety in the central nervous system are believed to be noradrenaline, 5HT (serotonin), GABA (Gamma-aminobutyric acid) and dopamine. The bulk of symptoms are mediated by the ANS (Autonomic nervous system), particularly the sympathetic nervous system. The modulation of fear and anxiety is a

function of the brain. Patients with anxiety disorders have an amplified brain reaction to anxiety signals. The brain and paleomammalian cortex are connected to areas of the prefrontal cortex (PFC), and aberrant prefrontal-limbic activation can be corrected with pharmacological or psychological treatments **[17]**. One or more of the modulatory stages involved have been connected to a number of molecular pathways. Serotonergic and nor-adrenergic neurotransmitter systems are the two that are most frequently mentioned. In general, it is believed that the noradrenergic system is overactive and the serotonergic system is underactive. These systems control other pathways and neuronal circuits in different parts of the brain, and as a result, level of stress and the overwhelming feeling of this stimulation are downregulated. Several individuals think that its emergence is due to reduced 5HT system activity and excessive noradrenergic system activity **[18]**.

ANXIETY TREATMENT

Anti-anxiety drugs have been used by people for generations. The very first anxiolytics was ethanol, which is still employed today. Other medications that were popular in the early half of the 20th century and some of which are still in use today include barbiturates and carbamate. Mild anxiety may be treated with benzodiazepines. Chronic anxiety is treated with psychotherapy, medication, or a combination of the two. Pharmacotherapy for anxiety disorders includes benzodiazepines, tricyclic antidepressants, SSRIs, SNRIs, moderate tranquillizers, and β –blockers **[19]**.

CLASSIFICATION:

1. Benzodiazepines: Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Alprazolam, Clonazepam
2. Azapirones: Buspirone, Gepirone, Isapapirone
3. Sedatives: Hydroxyzine
4. Barbiturates: Thiopental, Pentobarbital, Phenobarbital
5. Beta blockers: Propranolol
6. Antidepressants: –

- SSRIs: Fluoxetine, Fluvoxamine, Paroxetine, Escitalopram
- Serotonin and noradrenaline reuptake inhibitors (SNRIs): Duloxetine, Venlafaxine
- Benzodiazepine Antagonist: Flumazenil

BENZODIAZEPINES – DIAZEPAM

Diazepam is a benzodiazepine that has a long half-life and acts quickly. It is commonly used to treat seizures, severe anxiety, alcohol withdrawal, and panic disorders.

Brands include Diastat, Valium, and Valtoco 5 Mg Dose Kit.

PROCESS OF ACTION

The following mechanism describes how the benzodiazepine tranquillizer, diazepam, which has seizure, tranquilizer, pain reliever, and memory impairment characteristics, functions. Different receptors in the brain and spinal cord are where diazepam and other benzodiazepines bind. GABA Gamma-aminobutyric acid's inhibitory actions are strengthened by this binding. The central nervous system activity of GABA enhances sleep. Moreover, it controls neural activity, hallucination, remembering, stress, and seizures **[20]**.

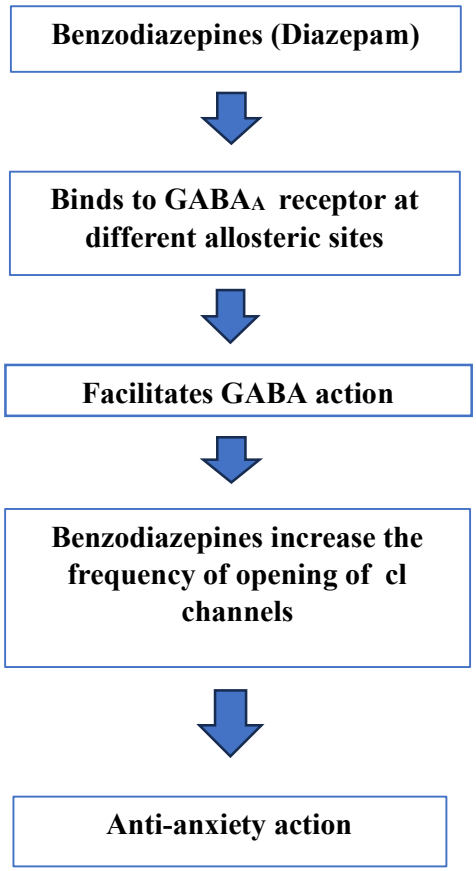

Figure 1: Mechanism of action

PHARMACOKINETICS:

Absorption: The highest possible plasma concentrations of diazepam normally take one hour to achieve after an oral dose has been absorbed greater than 90% of the time. Administration with food slows and decreases absorption. Diazepam is a very lipophilic drug that is widely available. Despite having a relatively rapid start to the action, the medication relocates rapidly. Benzodiazepines as well as their by-products are found in breast milk and cross the blood-brain and placental barriers. The distribution volume ranges from 0.8 to 1.0 L/kg. Desmethyl-diazepam is the most noteworthy active metabolite of diazepam,

which is produced predominantly by the mitochondrial enzymes CYP3A4 and CYP2C19. After the initial dispersion, the final elimination is prolonged. N-desmethyldiazepam, the final elimination half-life of the active metabolite is up to hundred hours. The most of diazepam and its derivatives are eliminated in the urine. Diazepam accumulates after repeated dosages, which causes its final elimination half-life to be a little slightly longer **[21]**.

ADVERSE EFFECTS:

In addition to the Neurological and bronchial impairment that are typical adverse effects of benzodiazepine, diazepam can also result in dependency and benzodiazepine withdrawal syndrome. Respiratory depression, Bradycardia, hypotension, syncope, symptoms of withdrawal, are all indications of abuse, dependency, and suicidality. Diazepam also has a number of other dangerous adverse effects.

DRUG INTERACTIONS:

Fluoxetine, chloramphenicol, and other drugs (ketoconazole, protease inhibitors, erythromycin) that block the CYP2C19 and CYP3A4 enzymes over an extended period of time may cause high diazepam levels. Prednisone and rifampin both stimulate CYP2C19, whereas carbamazepine, topiramate, phenytoin result in lower levels **[22]**.

OTHER ANTI-ANXIETY DRUGS

Buspirone: Buspirone is a weak tranquillizer that takes around two weeks to start functioning when compared with benzodiazepines. It benefits from having fewer sedative effects, is not addictive, and causes little withdrawal symptoms. For GAD, it works nicely. Buspirone's pharmacokinetics require that the dose be divided at least two days, which may make it difficult for patients to stick to their regimen. When SRIs are a concern for people with mild to moderate GAD, buspirone may be utilised as a first-line therapy **[23]**.

Beta blockers: Atenolol and propranolol, β blockers, are used to treat the physical manifestations of anxiety, such as a rapid heartbeat, trembling voices, sweating, headache, and quivering lips. For phobias, particularly social phobia, they are highly beneficial **[24]**.

SSRIs(Selective serotonin reuptake inhibitor): All anxiety disorders benefit from the use of selective serotonin reuptake inhibitors like fluoxetine, sertraline, paroxetine. They increase overall serotonergic transmission by selectively blocking SERTs which usually boost serotonergic neurotransmission by returning serotonin to the neuron for recycling. Desensitization of postsynaptic serotonin receptors in the raphe nucleus of the brainstem is one of the downstream effects of this process that is hypothesised to

contribute to the treatment of depression and anxiety **[25]**.

SNRIs(Serotonin–norepinephrine reuptake inhibitor: venlafaxine and duloxetine are also regarded as first line treatments, especially for Generalized anxiety disorder. In addition to raising norepinephrine levels by inhibiting nor-epinephrine transporter activity **[26]**.

Tricyclic antidepressants(TCAs): Imipramine, amitriptyline are tricyclic antidepressants that are effective in treating anxiety disorders but have serious side effects. They function by directly regulating particular 5-HT receptors, binding to the serotonin transporter and blocking of these receptors. However, because of their particularly nonselective receptor affinities, they have a number of harmful effects. TCAs' antagonistic actions on muscarinic acetylcholine receptors can result in considerable sore throat, diarrhoea, urinary retention, blurred vision, arrhythmia, and cognitive decline **[27]**.

CONCLUSION:

The set of mental health issues known as anxiety disorders can significantly affect a person's life. Excessive anxiety, concern, or unease over regular occurrences or events define these illnesses. Generalized anxiety disorder, panic disorder, social anxiety disorder, and particular phobias are only a few of the several types of anxiety disorders. Effective therapies for anxiety disorders are available, including a mix of medication and therapy. In addition to teaching coping mechanisms and assisting people in altering their negative thought patterns, counselling can also aid with symptom management. To manage anxiety problems and enhance general quality of life, assistance must be sought. If you or someone you love is struggling, it's critical to seek support and advice from a healthcare expert.

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