

**STRESS AND ITS MANAGEMENT THROUGH ANTI ANXIETY DRUGS: A REVIEW**

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**Summary**

Anxiety and stress are the most common factors for many of the diseases and disorders. The use of antianxiety drugs to relieve certain neurotic symptoms, involves decision making at the level of individual organism. In medical usage “anxiety denotes a state caused by an internal danger, while “fear” is a response to an external danger. “Stress” is the sum total of the bodily responses which occur when the organism has to adapt to a change. The antianxiety drugs relieve anxiety and certain other neurotic symptoms, stress, depression, fear or anxiety caused by schizophrenia and other psychiatric disorders. The antianxiety drugs are now being most frequently prescribed for the relief and prevention of emotional distress that might accompany a physical disorder. Somatic illness can cause stress and fear, but does not usually induce neurotic anxiety. In-patient suffering from physical disorder, treatment with anxiety drugs is justified only in the presence of psychoneurotic condition.

In the present review we have attempted to characterize the types of an anxiety and it's etiology, the various reasons for stress and anxiety, list of Benzodiazepines as a choice of drugs or the only way of treating stress. Stress management attracts all the physicians and the psychiatrics to have healthy and peaceful life.

**Keywords:** Antianxiety, stress, schizophrenia, depression.

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### **Introduction**

An anxiety disorder involves an excessive or inappropriate state of arousal characterized by feelings of apprehension, uncertainty or fear. The word is derived from the Latin, *angere*, which means to stroke or strangle. The anxiety response is often not attributable to a real threat.<sup>1</sup> Anxiety disorders have been classified according to the severity and duration of their symptoms and specific behavioral characteristics. Categories include:

1. Generalized anxiety disorder (GAD), which is long lasting and low-grade
2. Panic disorder, which has more dramatic symptoms
3. Phobias
4. Obsessive-compulsive disorder (OCD)
5. Post-traumatic stress disorder (PTSD)
6. Separation anxiety disorder (which is almost always seen in children)

GAD and panic disorder are the most common. Anxiety disorders are usually caused by a combination of psychological, physical, and genetic factors, and treatment is, in general, very effective<sup>2</sup>. Stress is an emotionally disruptive or upsetting condition of mind which occurs in response to adverse external influences. Stress raises the level of Adrenaline and corticosterone in the body, which leads to an increase in the heart rate, respiration and blood pressure and puts more physical stress on bodily organs. When something pleasant or unpleasant happens around you, which puts you in a state of strain or pressure, it is called stress. Various other concepts linked to the word stress are Anxiety, Depression, Exhaustion, Frustration, Despair, overwork. The nature of stress are broadly of two types:

1. Eustress (Positive stress)
2. Distress (Negative stress)

Both may not necessarily occur due to positive and negative events compulsorily. The reason being the distinction between good or bad depends upon the perception of an individual. The various types of stress are further categorized. Stress functions at three stages namely<sup>3</sup>

1. Alarm stage
2. Resistance stage
3. Exhaustion

## CAUSES OF ANXIETY DISORDER

A person's genetics, biochemistry, environment, history, and psychological profile all seem to contribute to the development of anxiety disorders. Most people with these disorders seem to have a biological vulnerability to stress, making them more susceptible to environmental stimuli than the rest of the population.

### A) Biochemical Factors

#### a) Abnormalities in the Brain.

Important research in anxiety disorders is focusing in the *amygdala*, which is sometimes referred to as the "fear center"<sup>4</sup>. This part of the brain regulates fear, memory, and emotion and coordinates these resources with heart rate, blood pressure, and other physical responses to stressful events. Some evidence suggests that the amygdala in people with anxiety disorders is highly sensitive to novel or unfamiliar situations and reacts with a high stress response.

OCD is the anxiety disorder most strongly associated with specific brain dysfunction. For example, abnormalities in a specific pathway of nerves have been linked to OCD, attention deficit disorder, and Tourettes syndrome. The symptoms of the three disorders are similar and they often coexist.

#### b) Neurotransmitters.

Studies suggest that an imbalance of certain substances called *neurotransmitters* (chemical messengers in the brain) may contribute to anxiety disorders. The neurotransmitters targeted in anxiety disorders are gamma-aminobutyric acid (GABA)<sup>5</sup>, serotonin, dopamine, and epinephrine. Serotonin appears to be specifically important in feelings of well-being, and deficiencies are highly related to anxiety and depression<sup>2</sup>.

Examples of study findings on some neurotransmitters are the following:

- Abnormalities in the neurotransmitters gamma-aminobutyric acid (GABA) and serotonin may have a particular role in susceptibility to generalized anxiety disorder. GABA helps prevent nerve cells from over-firing and serotonin is a brain chemical important in feelings of well-being.
- Serotonin is a major player in OCD.
- Changes in serotonin and dopamine have been observed in social phobia.
- People with post-traumatic stress disorder have abnormalities in stress hormones (cortisol) and neurotransmitters associated with stress (epinephrine and norepinephrine). Such

imbalances could account for the higher anxiety levels and a tendency to startle easily after a threat in people with PTSD.

**c) Abnormalities in Breathing Functions.**

Many people, including children, with anxiety disorders are very sensitive to the effects of carbon dioxide (CO<sub>2</sub>). Such people generally have higher than normal levels of cortisol--the major stress hormone. In such cases, exposure to excessive CO<sub>2</sub> causes these individuals to *hyperventilate*, in which their breathing becomes rapid and their heart rate quickens. Such a response also occurs during danger. Over time, then, a series of such responses creates a pattern of impaired breathing and a sense of panic that evolves into a full-fledged anxiety disorder. Since CO<sub>2</sub> is released from the lungs when people exhale, the condition may be aggravated in crowded spaces, such as airplanes or elevators.

**B) Genetic Factors<sup>6</sup>**

Up to 50% of people with panic disorder and 40% of patients with generalized anxiety (GAD) have close relatives with the disorder. (About half of GAD patients also have family members with panic disorder, and about 30% have relatives with simple phobias.) One study reported the risk for inheriting a major phobia ranges from 25% to 37%. OCD is also strongly related to a family history of the disorder. Researchers are looking for specific genetic factors that might contribute to an inherited risk. Of particular interest are possibly defective genes that regulate specific neurotransmitters, including serotonin and dopamine, which may cause people to become more afraid than others in response to a threat.

**C) Family Dynamics<sup>6</sup>**

The influence of the family on anxiety is complicated by both genetic and psychological factors.

**1) Panic Disorder and Family Influence.**

Certain psychodynamic theories suggest, and a few studies support the idea, that some people may develop panic disorder if they cannot resolve the early childhood conflict of dependence vs. independence. In one study, for example, young adults who had experienced childhood anxiety were more likely to live with their parents until their early to mid-twenties. Many people with panic disorder perceive their parents as being extremely controlling and overly protective while showing little actual affection.

**2) Phobias and Family Influence.**

Several studies show a strong correlation between a parent's fears and those of the offspring. Although an inherited trait may be present, some researchers believe that many children can "learn" fears and phobias, just by observing a parent or loved one's phobic or fearful reaction to an event. People who have social phobias and severe agoraphobia generally report less parental affection and more strictness, overprotection, and encouragement of dependence than those without these disorders. One 2000 study found similar traits in parents of children with social phobias. Such parents were also likely to have social phobias and depression.

**3) Obsessive Compulsive Disorder and Family Influence.**

One study found that parental influence played no part in obsessive-compulsive disorder if the OCD patient was also not suffering from depression. It should be noted, however, that depression coexists in two-thirds of OCD patients, and in the study patients who had both OCD and depression reported lower levels of parental care and overprotectiveness.

**D) Traumatic Events<sup>7</sup>**

Traumatic events generally trigger anxiety disorders in individuals who are susceptible to them because of psychological, genetic, or biochemical factors. The clearest example is post-traumatic stress disorder. Specific traumatic events in childhood, particularly those that threaten family integrity, such as spousal or child abuse, can also lead to other anxiety and emotional disorders. Some individuals may even have a biological propensity for specific phobias, for instance of spiders or snakes, that have been triggered and perpetuated after a single exposure.

**E) Medical Conditions<sup>8</sup>**

Although no causal relationships have been established, certain medical conditions have been associated with panic disorder. They include migraines, obstructive sleep apnea, mitral valve prolapse, irritable bowel syndrome, chronic fatigue syndrome, and premenstrual syndrome.

**F) PANDAS<sup>9</sup>**

The acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus) is a term for an autoimmune condition associated with group A streptococcal infection in children (the cause of "strep throat" and rheumatic fever). Children with PANDAS develop tic-related disorders, including OCD and Tourettes syndrome. In such cases, the OCD symptoms develop abruptly soon after the infection. It is unlikely to be an important cause of OCD.

**TREATMENT OPTIONS FOR SPECIFIC ANXIETY DISORDER**

<b>Treatment Options for Specific Anxiety Disorders</b>		
<b>Anxiety Disorder</b>	<b>Medications</b>	<b>Cognitive-Behavioral Therapy (CBT) and other Non-Drug Therapies</b>
<b>Generalized Anxiety Disorder<sup>2</sup></b>	Antidepressants, benzodiazepines, and buspirone are helpful but have varying side effects. Investigational drugs include pregabalin and other anticonvulsants.	Cognitive-behavioral therapy or anxiety management therapy. Anxiety management therapy involves education, relaxation training, and exposure to anxiety-provoking stimuli but does not include cognitive restructuring.
<b>Panic Attacks<sup>8</sup></b>	SSRIs are treatment of choice. If patients do not respond to SSRIs, short-term treatment with a benzodiazepine may be used, or patients may switch to another type of antidepressant such as venlafaxine or tricyclics.	Cognitive-behavioral therapy, provided in 12 - 16 sessions over 3 - 4 months, focuses on recreating fear symptoms and helping patients change their response to them.
<b>Social Anxiety Disorder<sup>10</sup></b>	SSRIs or venlafaxine are first-line drug treatments. Benzodiazepines may help patients who do not respond to these antidepressants. In severe cases, an MAOI antidepressant may be prescribed. Anticonvulsants such as gabapentin (Neurontin) and pregabalin (Lyrica) are being investigated.	Cognitive-behavioral therapy can help improve symptoms after 6 - 12 weeks.

<p><b>Obsessive-Compulsive Disorder<sup>11</sup></b></p>	<p>SSRIs are the first choice for adults. Clomipramine (a tricyclic antidepressant) is an alternative for adult patients who do not respond to SSRIs. For children, SSRIs do not seem to work as well for OCD as for other types of anxiety disorders.</p>	<p>Cognitive-behavioral therapy is the first treatment choice for children. For adults, either CBT or drug therapy may be offered as initial treatment. CBT techniques focus on exposure and response prevention (ERP).</p>
<p><b>Post-Traumatic Stress Disorder<sup>12</sup></b></p>	<p>Antidepressants, particularly SSRIs (sertraline and paroxetine approved for PTSD). The atypical antipsychotic olanzapine may be added to an antidepressant for patients who do not respond to a SSRI alone.</p>	<p>Trauma-focused psychological treatments include exposure therapy, trauma-focused cognitive therapy, and eye movement desensitization and reprocessing.</p>
<p>Note: For anxiety disorders in adults, the most effective treatments are usually combinations of drugs and CBT techniques. For children, CBT is usually the first treatment.</p>		

**Table No.1- Treatment options for specific Anxiety Disorder**

MECHANISM OF ACTION OF ANTIANXIETY DRUGS<sup>3,13</sup>

Based on the XBD173 bond on the translocator protein 18 in the mitochondrial membrane, the absorption of the neurosteroid precursor cholesterol is intensified and increased volumes of neurosteroids are metabolised. These neurosteroids alter the function of a receptor on the post-synaptic membrane of nerve cells. This hinders signal forwarding and triggers an anxiolytic effect at behaviour level.

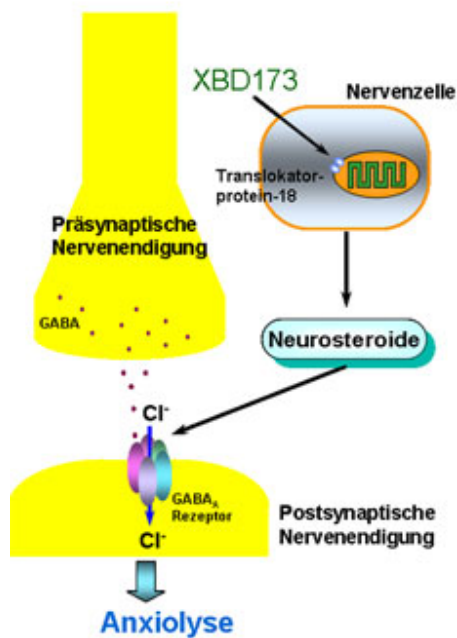


Figure No.1- Mechanism of action of anti-anxiety drugs



## CURRENTLY AVAILABLE ANTIANXIETY DRUGS

A) Benz odiazepines<sup>14,15</sup>

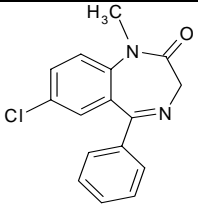
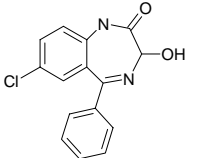
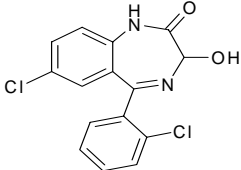
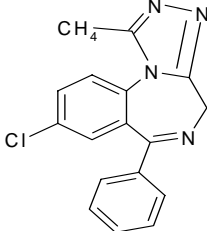
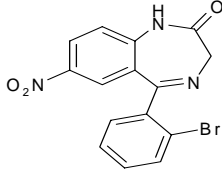
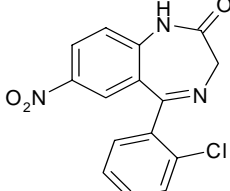
Generic name	Structure	Brand name	Common effects
Diazepam		Antenex, Diazemuls (injectable) Ducene, Valium	relieves anxiety; can increase depression
Oxazepam		Alepam, Serepax , Murelax	relieves anxiety; can increase depression; shorter half life than diazepam
Lorazepam		Ativan	Muscle relaxant, mood elevators, CNS depressant
Alprazolam		Kalma, Ralozam, Xanax	Calming activity, induces sleep
Bromazepam		Lexotan	relieves anxiety; can increase depression
Clonazepam		Klonopin	For the short term relief of mild to moderate anxiety

Table No.2-Currently available Benzodiazepines

**B) Sedative Hypnotic Drugs<sup>1,15</sup>**

Generic name	Brand name	Common effects and side effects
Nitrazepam	Alodorm, Mogadon	Induces sleep; “hangover effect” - drowsiness and impaired motor coordination may persist over more than a day; interacts with other psychotropic drugs
Temazepam	Normison, Nocturne, Nomapam, Euhypnos, Temaze, Temtabs	Hastens onset of sleep and increased total sleeping time; addictive benzodiazepine so should not be used for long periods.
Triazolam	Halcion	Short acting and powerful sleep inducer; at higher doses (more than 0-5mg) memory loss for events of night before; addictive benzodiazepine; fewer “hangover” effects but can cause morning irritability
Chlormethiazole	Hemineurin M	Sedative/hypnotic with anticonvulsant effect; nasal irritation
Flunitrazepam	Hypnoderm, Rohypnol	Induces sleep in severe insomnia; addictive benzodiazepine
Midazolam	Hypnovel	Short acting anaesthetic: induces sedation, hypnosis, amnesia and anaesthesia; increases sedative effect of other psychotropic drugs
Zopiclone	Imovane	Reduces tolerance to alcohol, short acting hypnotic; can impair driving ability and motor coordination
Amylobarbitone	Neur-Amyl	Barbiturate, dangerous in overdose
Diphenhydramine	Unisom Sleepgels	Antihistamine drug which can induce sleep; increases the effect of alcohol and other psychotropic drugs

**Table No.3- Sedative Hypnotic Drugs**

**C) Antidepressant****a) SSRI Antidepressant drugs<sup>16,17</sup>**

Generic name	Brand name	Common side effects
Paroxetine	Aropax	Nausea, sexual dysfunction for both men and women, gastrointestinal problems; can trigger mania
Fluoxetine	Prozac, Erocap, Lovan, Zactin	weight loss, can trigger mania; can increase agitation; sexual dysfunction; can increase the effect of other psychotropic drugs; should not be taken with MAOI drugs;
Citalopram	Cipramil	Increases alertness, reduces fatigue
Venlafaxine	Efexor	Can trigger mania or hypomania; can increase blood pressure; dizziness, gastrointestinal problems; sexual problems
Fluvoxamine	Luvox	Nausea, drowsiness, anorexia, sexual dysfunction
Sertraline	Zoloft	Weight loss; sexual dysfunction; diarrhoea

**Table No.4- SSRI Antidepressant drugs****b) Tricyclic Antidepressants<sup>18,19,21</sup>**

The antidepressant drugs known as tricyclic antidepressants (TCAs) have also been effective in treating panic and obsessive-compulsive disorders. Studies on specific TCAs have suggested the following benefits:

- Imipramine (Tofranil, Janimine) is the most commonly used TCA for panic disorder. It is also effective in treating agoraphobia and GAD. In one study it was helpful in reducing side effects during withdrawal from benzodiazepines, the standard anti-anxiety agents.
- Doxepin (Adapin, Sinequan) has been beneficial for people with a mix of generalized anxiety disorder and depression.
- Clomipramine (Anafranil) is also effective for panic disorders and has been approved for OCD. The drug causes significant reduction in OCD symptoms for patients, including

some children, who can tolerate it. (The other tricyclics do not appear to benefit OCD patients.) Many patients stop using Anafranil, however, because of side effects. Many of those who stay on the drug experience adverse effects.

**Side effects of TCA**

Sleep disturbance, abrupt reduction in blood pressure upon standing, weight gain, sexual dysfunction, and mental disturbance. Elderly patients and those with a history of seizures, cardiac problems, closed-angle glaucoma, and urinary retention or obstruction should be closely supervised when taking tricyclics.

**c) Monoamine Oxidase Inhibitors<sup>20</sup>**

Monoamine oxidase inhibitors (MAOIs), typically phenelzine (Nardil) or tranylcypromine (Parnate), are antidepressants used for panic disorder or OCD that does not respond to other treatments. Moclobemide (Manerix, Aurorix) is a newer MAOI available in Canada and Europe that showed some benefits for social phobias in some, but not all studies..MAOIs commonly cause weight gain, drowsiness, dizziness, sexual dysfunction, and insomnia. The primary problem with most of these agents is the need for dietary restrictions. Severe hypertension can be brought on by eating certain foods that have a high tyramine content, including cheese, red wine, vermouth, dried meats and fish, canned figs, and fava beans. MAOIs can also lead to serious hypertensive interactions with certain drugs, including some common over-the-counter cough medications and decongestants. They can also cause birth defects and should not be taken by pregnant women.

**D) Azapirones<sup>3</sup>**

Azapirones, including, buspirone (BuSpar) and gepirone (Ariza, Variza), act on serotonin receptors call 5-HT (1A). Buspirone has been the most intensively studied. It appears to be as effective as a benzodiazepine for treating generalized anxiety disorder. Some experts also think it may be useful for adolescents and children. It usually takes several days to weeks for the drug to be fully effective, and it is not useful against panic attacks.

It should be noted that the drug does not produce any immediate euphoria or change in sensation, so some people believe, erroneously, that the drug doesn't work. Such qualities result in a very low potential for abuse. In fact, unlike the benzodiazepines, buspirone is not addictive, even with long-term use, so it may be particularly useful for the patient whose anxiety disorder coexists with alcoholism or drug abuse.

Buspirone also seems to have less pronounced side effects than benzodiazepines and no withdrawal effects, even when the drug is discontinued quickly. Common side effects include dizziness, drowsiness, and nausea. BuSpar should not be used with monoamine oxidase inhibitors (MAOIs).

**E) Beta-Blockers<sup>3</sup>**

Beta-blockers, including propranolol (Inderal) and atenolol (Tenormin), block the nerves that stimulate the heart to beat faster. They affect only the physiologic symptoms of anxiety and are most helpful for phobias, particularly performance anxiety. Beta-blockers are less effective for other forms of anxiety.

**F) Clonidine<sup>1</sup>**

Clonidine, a drug that relaxes blood vessels, has been used to treat children with post-traumatic stress disorder. Some experts believe it should be tried for anxiety disorders if other therapies fail. The drug can have severe side effects.

**G) Atypical Antipsychotics<sup>22,23</sup>**

In certain severe cases, agents called atypical antipsychotics may be useful. They include risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Zeldox, Geodon), and others. In one study, risperidone was useful in combination with an SSRI for OCD patients who did not respond to an SSRI alone. They also may be useful for severe GAD. Common side effects include sleepiness and dizziness. Most cause weight gain. In high doses they may cause *extrapyramidal* symptoms, which involve the nerves and muscles controlling movement and coordination. The risk for these side effects, however, are far less than with older antipsychotic agents.

**Drugs Being Evaluated for Anxiety States<sup>24,25</sup>**

**Gabapentin and Other Anti-Epileptic Agents**

Gabapentin is a drug used for epilepsy. Small studies suggest it may be useful for certain anxiety disorders, such as social phobia and post-traumatic stress disorder. It may also be helpful during withdrawal from benzodiazepines. Pregabalin is an investigative agent that is similar to gabapentin and is showing promise for social phobia, panic disorder, and generalized anxiety disorders.

**Hydroxyzine. Hydroxyzine (Atarax, Vistaril)**

It is an antihistamine used to treat itching from allergies. In one well-conducted 2003 study, it was as effective as a benzodiazepine for treating GAD.

**Prazosin. Prazosin (Minipress)**

It is known as an alpha (or adrenergic) blocker. It reduces blood pressure and is sometimes used in benign prostate hyperplasia. Studies are supporting its effectiveness for alleviating nightmares and other symptoms in people with PTSD.

**Immunotherapies for Strep-Related Obsessive-Compulsive Disorder<sup>24</sup>**

In cases of OCD originating with a strep throat infection during childhood, some studies are using therapies that affect the immune system. They include immunoglobulin treatments (injections of certain antibody groups), penicillin, corticosteroids (prednisone), and plasmapheresis (blood exchange). In one study, children with a first episode of OCD related to strep throat were treated with antibiotics, and OCD symptoms resolved in all of them. Other studies using antibiotics on patients with long-standing OCD have not reported success.

**Warnings for Alternative and so-called Natural Remedies used in Anxiety Disorders<sup>26</sup>**

Many people are attracted to herbal or so-called natural remedies to relieve anxiety. Alternative or natural remedies are not regulated and their quality is not publicly controlled. In addition any substances that can affect the bodies chemistry can, like any drug, produced side effects that may be harmful. Herbal or natural remedies used for anxiety may cause problem in certain cases:

**Valerium:** Sedative, listed on the FDA's list of generally safe products, but effects could be dangerously increased if it is used with standard sedative.

**Side effect:** vivid dreams, high doses cause Blurred vision, excitability.

**Kava:** May relieve anxiety, has side effects, some very severe of major concern are reports of liver failure and death from this medication.

**Side effects:** Itchy scaly skin, muscle weakness, and problem with co ordination. Interacts dangerously with Alprazolam increases potency of other drugs including other sleep medication, alcohol, and antidepressant.

**Aromatherapy:** Associated with skin allergies.

### Conclusion

There have been tremendous advances in the development of the atypical antianxiety. Since last decade, new generation antianxiety drugs have shown clear improvement and protection against the affective cognitive symptoms. However some of these agents cause adverse effects such as weight gain and sexual dysfunction yet, they have more side effects profile. Various novel compounds under development antianxiety agents have created hope for patients with anxiety and depression and their families helping them to obtain a more positive out look of life and future.

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