



Anxiety disorder: An overview

Jain Akash *, Sharma Rishu and Gahalain Nidhi

M.M. College of Pharmacy, M.M.University, Mullana, Ambala, India

Abstract

Anxiety is a psychological disorder characterised by persistent and disproportionate fear unrelated to any genuine risk. Preclinical studies have shown that the amygdala plays a key role in fear circuitry, and that abnormalities in amygdala pathways can affect the acquisition and expression of fear conditioning. Drugs such as glutamate *N*-methyl- D-aspartate (NMDA) antagonists, and blockers of voltage-gated calcium channels, in the amygdala, may block these effects. The original treatment indicated for those suffering from neurotic anxiety was to employ psychotherapy to facilitate changes in behaviour and coping with stressful events. The Food and Drug Administration originally approved many gamma-aminobutyric acid (GABA) facilitating drugs since the 1960s for anxiety treatment. This review reveals the underlying pathophysiology and drug therapy of anxiety disorder.

Keywords: Anxiety, Gamma-aminobutyric acid (GABA), Phobias, Benzodiazepines.

Introduction

Anxiety disorders are a group of mental health problems. They include generalised anxiety disorders, social phobias, specific phobias (for example, agoraphobia and claustrophobia), panic disorders, obsessive compulsive disorder (OCD) and post traumatic stress disorder^[1]. Anxiety is a feeling of uneasiness, uncertainty or fear, in response to a real or imagined danger^[2]. The body responds to anxiety by releasing a number of "stress" hormones, like adrenaline and cortisol, which have an effect on almost every organ in the body. Untreated anxiety disorders can lead to depression^[3].

Symptoms of anxiety disorders

Physical symptoms of anxiety disorders are due to released stress hormones. These may increase blood pressure, cause heart palpitations, chest pain, rapid breathing or breathlessness, sweating, increased muscle tension or irritability. Intestinal blood flow decreases, resulting in nausea or diarrhoea. There is often a decreased sex drive. Children may also have a fear of being away from the family, a refusal to go to school, a fear of strangers, a fear of falling asleep or have recurrent nightmares^[3].

Types of anxiety disorders

A number of anxiety disorders have been classified.

1. Panic Disorder

People with panic disorder experience recurrent, unexpected attacks of intense anxiety or terror usually lasting 15 to 30 minutes. These attacks reach peak intensity within seconds and then subside over 5 to 20 minutes. Episodes of terror are accompanied by shortness of breath, rapid heartbeat (palpitations), chest pain, hot flushes or chills, nausea, dizziness, abdominal cramps, sweating, shakiness, a choking feeling, feelings of unreality, and fears of dying or going insane. Frequency of attacks can vary widely, and may occur spontaneously or in response to a particular situation^[4-5].

2. Phobias^[4-8]

Phobias are persistent, irrational fears of certain objects or situations. The main symptom of this disorder is the excessive and unreasonable desire to avoid the feared stimulus. Psychologists and psychiatrists classify most phobias into three categories and according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), such phobias are considered to be sub-types of anxiety disorder. The three categories are:

* Corresponding Author:

E-mail: akash2911@gmail.com, Ph – 09729928104

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1. **Social phobia**- Fears involving other people or social situations such as performance anxiety or fears of embarrassment by scrutiny of others, such as eating in public. Overcoming social phobia is often very difficult without the help of therapy or support groups. Social phobia may be further subdivided into :
 - (a) Generalized social phobia (also known as social anxiety disorder or simply social anxiety).
 - (b) Specific social phobia, in which anxiety is triggered only in specific situations. The symptoms may extend to psychosomatic manifestation of physical problems. For example, sufferers of paruresis find it difficult or impossible to urinate in reduced levels of privacy. This goes far beyond mere preference: when the condition triggers, the person physically cannot empty their bladder.
2. **Specific phobias** - Fear of a single specific panic trigger such as spiders, snakes, dogs, water, heights, flying, catching a specific illness, etc. Many people have these fears but to a lesser degree than those who suffer from specific phobias. People with the phobias specifically avoid the entity they fear.
3. **Agoraphobia** – A generalized fear of leaving home or a small familiar 'safe' area, and of possible panic attacks that might follow. May also be caused by various specific phobias such as fear of open spaces, social embarrassment (social agoraphobia), fear of contamination (fear of germs).

3. Post-Traumatic Stress Disorder (PTSD)

PTSD is an extremely debilitating condition that occurs after exposure to intensely frightening events or experiences in which severe physical harm was threatened or occurred. These events include violent personal assaults such as rape, mugging, disasters, car accidents or military combat. These people repeatedly re-live the ordeal in the form of mental flash backs, nightmares or disturbing thoughts or memories, especially when reminded of the trauma. Symptoms can occur weeks, months or even years after the traumatic event. Symptoms of PTSD include emotional numbness or withdrawal, hopelessness, mood swings, sleep disturbances, depression, irritability, outbursts of anger, feelings of intense guilt, inability to concentrate and an excessive startle response to noise^[4, 9, 10].

4. Obsessive-Compulsive Disorder (OCD)

People with OCD suffer from repeated, unwanted thoughts or mental images (obsessions) which may result in compulsive behaviour - repetitive, uncontrollable routines performed in the hope of preventing the obsessive thoughts or making them go away. Rituals such as hand washing, counting or checking are common. These rituals, however, provide only temporary relief, and not performing them markedly increases anxiety. OCD is time-consuming, distressing, and can disrupt normal functioning^[4, 11-13].

5. Generalised Anxiety Disorder (GAD)

People with GAD suffer from an almost constant state of tension and anxiety lasting more than 6 months, without an obvious cause for the anxiety. They usually expect the worst, worrying uncontrollably about money, health, family or work. They are constantly on edge, have difficulty concentrating and typically have physical symptoms such as fatigue, sleep disturbances, trembling, muscle tension, headaches, irritability or hot flushes. These symptoms cause much distress and impair normal functioning^[4, 11-13].

Pathophysiology

a) Neuromolecular:

Low levels of GABA, a neurotransmitter that reduces activity in the central nervous system, contribute to anxiety. A number of anxiolytics achieve their effect by modulating the GABA receptors^[14, 15, 16]. Severe anxiety and depression are commonly induced by sustained alcohol abuse which in most cases abates with prolonged abstinence. Even moderate, sustained alcohol use may increase anxiety and depression levels in some individuals^[17]. Caffeine, alcohol and benzodiazepines can worsen or cause anxiety and panic attacks^[18]. In one study in 1988–1990,^[19] illness in approximately half of patients attending mental health services at one British hospital psychiatric clinic, for conditions including anxiety disorders such as panic disorder or social phobia, was determined to be the result of alcohol or benzodiazepine dependence. In these patients, cessation of their anxiety symptoms corresponded with stopping the use of the benzodiazepine or alcohol. There is evidence that chronic exposure to organic solvents in the work environment can be associated with anxiety disorders. Painting, varnishing and carpet laying are some of the jobs in which significant exposure to organic solvents may occur^[20].

b) Amygdala:

The amygdala is central to the processing of fear and anxiety, and its function may be disrupted in anxiety disorders^[21]. Sensory information enters the amygdala through the nuclei of the basolateral complex (consisting of lateral, basal, and accessory basal nuclei).

The basolateral complex processes sensory related fear memories, and communicate their threat importance to memory and sensory processing elsewhere in the brain, such as the medial prefrontal cortex and sensory cortices. Another important area is the adjacent central nucleus of the amygdala, which controls species-specific fear responses, via connections to the brainstem, hypothalamus, and cerebellum areas. In those with general anxiety disorder, these connections functionally seem to be less distinct, with greater gray matter in the central nucleus. Another difference is that the amygdala areas have decreased connectivity with the insula and cingulate areas that control general stimulus salience, while having greater connectivity with the parietal cortex and prefrontal cortex circuits that underlie executive functions^[21]. The latter suggests a compensation strategy for dysfunctional amygdala processing of anxiety. Amygdalofrontoparietal coupling in generalized anxiety disorder patients may reflect the habitual engagement of a cognitive control system to regulate excessive anxiety^[21]. This is consistent with cognitive theories that suggest the use in this disorder of attempts to reduce the involvement of emotions with compensatory cognitive strategies. Anxiety processing in the basolateral amygdala has been implicated with dendritic arborisation of the amygdaloid neurons. SK2 potassium channels mediate inhibitory influence on action potentials and reduce arborisation. By over expressing SK2 (Small conductance calcium-activated K (potassium) channels) in the basolateral amygdala, anxiety in experimental animals can be reduced together with general levels of stress-induced corticosterone secretion^[22].

c) **Stress:**

Anxiety disorder can arise in response to life stresses such as financial worries or chronic physical illness. Anxiety is also common among older people who have dementia. On the other hand, anxiety disorder is sometimes misdiagnosed among older adults when doctors misinterpret symptoms of a physical ailment (for instance, racing heartbeat due to cardiac arrhythmia) as signs of anxiety^[23].

Treatment

- Behavioural therapy
- Pharmacological treatment
- Natural treatment

Behavioural therapy for anxiety disorders:^[24-26]

Cognitive-behavioural therapy and exposure therapy are two effective anxiety disorder treatments. Both are types of behavioural therapy, meaning they focus on behaviour rather than on underlying psychological conflicts or issues from the past. Behavioural therapy for anxiety usually takes between 5 and 20 weekly sessions.

Cognitive-behaviour therapy – As the name suggests, cognitive-behavioural therapy focuses on thoughts—or cognitions—in addition to behaviours. When used in anxiety disorder treatment, cognitive-behavioural therapy helps you identify and challenge the negative thinking patterns and irrational beliefs that are fuelling your anxiety.

Exposure therapy – In exposure therapy for anxiety disorder treatment, you confront your fears in a safe, controlled environment. Through repeated exposures, either in your imagination or in reality, to the feared object or situation, you gain a greater sense of control. As you face your fear without being harmed, your anxiety gradually diminishes.

Pharmacological treatment

Benzodiazepines

Benzodiazepine is a psychoactive drug whose core chemical structure is the fusion of a benzene ring and a diazepine ring. The first benzodiazepine, chlordiazepoxide, was discovered accidentally by Leo Sternbach in 1955, and made available in 1960 by Hoffmann–La Roche, which has also marketed diazepam since 1963^[27].

Classification

1. **Long acting benzodiazepines:** (half life more than 24 hours) Chlordiazepoxide, Diazepam, Clorazepate, Flurazepam^[28].
2. **Intermediate acting benzodiazepines:** (half life - 10-24 hours) Alprazolam, Lorazepam, Temazepam, Estazolam,^[28, 29].
3. **Short acting benzodiazepines:** (half life less than 10 hours) Triazolam, Midazolam, Oxazepam^[28, 30].

Mechanism of Action

The targets for benzodiazepine actions are the γ -aminobutyric acid (GABA_A) receptors. Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS). The fast-inhibitory activity of GABA is mediated by the GABA_A receptor, which acts as a molecular substrate for the regulation of vigilance, anxiety, muscle tension, epileptogenic activity and memory functions in the brain^[31, 32].

These receptors are primarily composed of α , β and γ subunit families of which a combination of five or more span the postsynaptic membrane. Depending on the types, number of subunits, and brain region localization, the activation of the receptors results in different pharmacologic effects^[32]. GABA_A receptors containing α_1 subunit mediate sedation and anterograde amnesia, and modulate seizure protection^[33, 34], whereas α_2 subunit-containing GABA_A receptors, but not those with α_3 subunits, mediate anxiolysis^[35-37]. Benzodiazepines modulate the GABA effects by binding to a specific, high-affinity site located at the interface of the α subunit and the γ_2 subunit. These binding sites are sometimes labelled benzodiazepine receptors. Two benzodiazepine (BZ) receptor subtypes commonly found in the CNS have been designated as BZ₁ and BZ₂ receptor depending on whether their composition includes the α_1 subunit or the α_2 subunit, respectively^[38,39]. Benzodiazepines produce their clinical effects via interactions with an allosteric modulatory site on the GABA_A receptor. Benzodiazepine binds to this site and act as positive allosteric modulators, potentiating the fast inhibitory effects of GABA on neurotransmission. This increases the frequency of chloride channel opening^[40]. The influx of chloride ions causes a small hyperpolarisation that moves the postsynaptic potential away from its firing threshold and, thus, inhibits the formation of action potentials resulting in inhibition of neuronal firing. Binding of a benzodiazepine to its receptor site will increase the affinity of GABA for the GABA-binding site (and vice versa) without actually changing the total number of sites. The clinical effects of the various benzodiazepines correlate well with each drug's binding affinity for the GABA receptor-chloride ion channel complex^[41].

Pharmacokinetic

Depending on their lipid-solubility, Benzodiazepines may cross the blood-brain barrier into the central nervous system. The time taken for this transfer from vascular space to the CNS represents the onset of action. High lipid-soluble drugs like diazepam have a faster onset of action, whereas less lipid-soluble agents like oxazepam have a slower onset of action. Duration of action is dependent on the redistribution of the drug from the CNS to the peripheral fat stores and the hepatic metabolism of the drug^[42]. Benzodiazepines are metabolized through a variety of hydroxylation, desalkylation, reduction, and acetylation reactions (phase I reactions), followed in many cases by conjugation to glucuronic acid (phase II reactions) before excretion^[28]. In most cases, the phase I metabolites have biological activity. Several Benzodiazepines may be considered pro-drugs, which are rapidly metabolized into active metabolites. Cytochrome P450 (CYP) enzymes in the liver are responsible for phase I drug metabolism. Phase II metabolism is less affected by liver disease and old age^[42,43].

Interactions

Benzodiazepines may have different interactions with certain drugs. Many drugs, including oral contraceptives, some antibiotics, antidepressants and antifungal agents, inhibit cytochrome enzymes in the liver. They reduce the rate of elimination of the benzodiazepines that are metabolized by CYP450, leading to possibly excessive drug accumulation and increased side effects. In contrast, drugs that induce cytochrome P450 enzymes, such as the antibiotic rifampicin and the anticonvulsants carbamazepine and phenytoin, accelerate elimination of many benzodiazepines and decrease their action^[44,45]. Taking benzodiazepines with alcohol, opioids and other central nervous system depressants potentiates their action. This often results in increased sedation, impaired motor coordination, suppressed breathing^[44, 45]. Antacids may slow down absorption of some benzodiazepines; however, this effect is marginal and inconsistent^[44].

Therapeutic uses

Benzodiazepines possess sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant, and amnesic actions, which are useful in a variety of indications such as alcohol dependence, seizures, anxiety, panic, agitation and insomnia^[46]. Benzodiazepines are also useful in the treatment of muscle spasms^[47], dental phobia^[48], parasomnia^[49]. Benzodiazepines are also used to treat the acute panic caused by hallucinogen intoxication^[50]. Rapid eye movement behaviour disorder responds well to low doses of clonazepam^[51,52].

Dependence

Various mechanisms for development of benzodiazepines tolerance and dependence and manifestations of benzodiazepines withdrawal is associated with the changes in the GABA_A /BZ receptor function, changes in the serotonin, noradrenaline, cholecystokinin, glutamate and acetylcholine neurotransmitter systems, altered brain metabolism, as well as altered function of calcium channels^[53]. Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and rarely, seizures^[54].

Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy. Benzodiazepines with a short elimination half-life, such as triazolam, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated, such as flurazepam^[55, 56]

Adverse Effects

The most common side-effects of benzodiazepines are related to their sedating and muscle-relaxing action. They include drowsiness, dizziness and decreased alertness and concentration. Lack of coordination may result in falls and injuries, particularly in the elderly^[57, 58]. Decreased libido and erection problems are a common side-effect. Hypotension and suppressed breathing may be encountered with intravenous use^[57, 58].

Paradoxical effects

Paradoxical reactions, such as increased seizures in epileptics^[59], aggression, violence, impulsivity, irritability and suicidal behaviour sometimes occur. These reactions have been explained as consequences of disinhibition that is loss of control over socially unacceptable behaviour^[60, 61]. However, they occur with greater frequency in recreational abusers, individuals with borderline personality disorder, children, and patients on high-dosage regimes^[62, 63]. In these groups, impulse control problems are the most important risk factor for disinhibition; learning disabilities and neurological disorders are also significant risks^[61]. Paradoxical effects may also appear after chronic use of benzodiazepines^[64].

Cognitive effects

The short-term use of benzodiazepines adversely affects multiple areas of cognition; most notably, it interferes with the formation and consolidation of memories of new material and may induce complete anterograde amnesia^[57]. Long-term use of benzodiazepines was associated with moderate to large adverse effects on all areas of cognition, with visuospatial memory being the most commonly detected impairment. Some of the other impairments reported were decreased IQ, visiomotor coordination, information processing, verbal learning and concentration^[65, 66].

Long-term effects

The long-term adverse effects of benzodiazepines include a general deterioration in physical and mental health and tend to increase with time. The adverse effects can include cognitive impairment, as well as affective and behavioural problems. Feelings of turmoil, difficulty in thinking constructively, loss of sex-drive, agoraphobia and social phobia, increasing anxiety and depression, loss of interest in leisure pursuits and interests, and an inability to experience or express feelings can also occur^[67, 68].

Contraindications

Because of their muscle relaxant action, benzodiazepines may cause respiratory depression in susceptible individuals. For that reason, they are contraindicated in people with myasthenia gravis, sleep apnea, bronchitis and COPD^[69]. Caution is required when benzodiazepines are used in people with personality disorders or mental retardation because of frequent paradoxical reactions^[69]. In major depression, they may precipitate suicidal tendencies and are sometimes used for suicidal overdoses^[69]. Benzodiazepines should be used cautiously in treating patients with liver disease. They should be avoided in patients with acute narrow-angle glaucoma. Alcohol and other CNS depressants enhance the sedative-hypnotic effects of the benzodiazepines^[70].

Pregnancy

Exposure to benzodiazepines during pregnancy has been associated with a slightly increased risk of cleft palate in newborns. Their use by expectant mothers shortly before the delivery may result in a floppy infant syndrome, with the newborns suffering from hypotonia, hypothermia, lethargy and breathing and feeding difficulties^[71]. Cases of neonatal withdrawal syndrome have been described in infants chronically exposed to benzodiazepines in utero. This syndrome may be hard to recognize as it starts several days after delivery, for example, as late as 21 day for chlordiazepoxide. The symptoms include tremors, hypertonia, hyperreflexia, hyperactivity and vomiting and may last for up to three to six months^[72].

Barbiturates

Barbiturates are a group of drugs in the class of drugs known as sedative-hypnotics, which generally describes their sleep-inducing and anxiety-decreasing effects. The first barbiturate, malonyl urea or barbituric acid, was synthesised in 1864 by Adolph von Baeyer from the condensation of malonic acid, derived from apples and urea^[73]. Barbiturates were first used in medicine in the early 1900s and became popular in the 1960s and 1970s as treatment for anxiety, insomnia, or seizure disorders. With the popularity of barbiturates in the medical population, barbiturates as drugs of abuse evolved as well.

Barbiturates were abused to reduce anxiety, decrease inhibitions and treat unwanted effects of illicit drugs. Barbiturates can be extremely dangerous because the correct dose is difficult to predict. Even a slight overdose can cause coma or death. Barbiturates are also addictive and can cause a life-threatening withdrawal syndrome. Barbiturate use and abuse has declined dramatically since the 1970s, mainly because a safer group of sedative-hypnotics called benzodiazepines are being prescribed (www.emedicinehealth.com).

Classification

1. **Long acting:** (Duration of action 1-2 days)-Phenobarbital^[74]
2. **Short acting:** (Duration of action 3-8 hours) - Pentobarbital, Secobarbital, Amobarbital^[74].
3. **Ultra-short-acting:** (Duration of action 20 minutes)-Thiopental^[74]

Mechanism of action

Barbiturates exert their CNS-depressant effects by both potentiating the inhibitory effects of GABA and suppressing excitatory effects of glutamate. However, suppression of excitatory neurotransmission does not contribute to their sedative/hypnotic effects^[75]. The principal mechanism of action of barbiturates is believed to be their affinity for the GABA_A receptor (Acts on GABA: BDZ receptor Cl⁻ channel complex). GABA is the inhibitory neurotransmitter in the mammalian central nervous system (CNS). The GABA_A receptor is a sub-type of GABA receptors which is classified as a ligand-gated ion channel meaning that the binding of a ligand to the receptor causes the ion channel to open^[76]. Barbiturates bind to the GABA_A receptor at the alpha subunit, which are binding sites distinct from GABA itself and also distinct from the benzodiazepine binding site. Like benzodiazepines, barbiturates potentiate the effect of GABA at this receptor. In addition to this GABA-ergic effect, barbiturates also block the AMPA receptor, a subtype of glutamate receptor. Glutamate is the principal excitatory neurotransmitter in the mammalian CNS. Taken together, the findings that barbiturates potentiate inhibitory GABA_A receptors and inhibit excitatory AMPA receptors can explain the CNS-depressant effects of these agents. At higher concentration they inhibit the Ca²⁺-dependent release of neurotransmitters^[76]. Barbiturates produce their pharmacological effects by increasing the duration of chloride ion channel opening at the GABA_A receptor (pharmacodynamics: this increases the efficacy of GABA), whereas benzodiazepines increase the frequency of the chloride ion channel opening at the GABA_A receptor (pharmacodynamics: this increases the potency of GABA). The direct gating or opening of the chloride ion channel is the reason for the increased toxicity of barbiturates compared to benzodiazepines in overdose^[75].

Pharmacokinetics

Barbiturates are absorbed orally and distributed widely throughout the body. The most important factor that plays a role in the entrance of a barbiturate into the brain is its lipid solubility. All barbiturates redistribute in the body from the brain to the splanchnic areas, to skeletal muscle, and finally, to adipose tissue^[74]. This movement is important in causing the short duration of action of thiopental and similar short-acting derivatives. They readily cross the placenta and can depress the foetus. Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine^[74].

Adverse effects

1. Drowsiness and impaired concentration^[74, 77].
2. **Drug hang-over:** Hypnotic doses of barbiturates produce a feeling of tiredness that lasts many hours after the patient awakes^[74, 77].
3. **Tolerance:** Induction of liver microsomal enzymes leads to tolerance as well as the decrease of the effect of drugs that are metabolized by hepatic enzymes, causing serious drug interactions; examples of such drug interactions:
 - Accelerated metabolism of vitamin K is observed in cases of coagulation defects in neonates whose mothers were taking Phenobarbital.
 - Hepatic enzyme induction enhances the metabolism of endogenous steroid hormones causing endocrine disturbances^[74].
4. **Dependence:** With regular use of barbiturates, barbiturate dependence develops^[78]. Barbiturate use can lead to both psychological and physical dependence and the drugs have a high abuse liability^[79]. The GABA_A receptor, one of barbiturates, main sites of action, is thought to play a pivotal role in the development of dependence on barbiturates, as well as the euphoric "high" that results from their abuse^[79]. Abrupt withdrawal of barbiturates causes severe withdrawal symptoms manifested as tremors, anxiety, restlessness, weakness, nausea, vomiting, seizures, and cardiac arrest that may lead to death^[74].

5. Over dosage: A barbiturate overdose results when a person takes a larger-than-prescribed dose of barbiturates. Symptoms of an overdose typically include sluggishness, in coordination, difficulty in thinking, slowness of speech, faulty judgment, drowsiness or coma, shallow breathing, staggering, and in severe cases coma and death. Barbiturates in overdose with other CNS depressants for example, alcohol, opiates or benzodiazepines is even more dangerous due to additive CNS and respiratory depressant effects. Barbiturate poisoning can be treated by artificial respiration, gastric lavage, and forced alkaline diuresis to accelerate elimination^[80, 81].

Interactions

Birth control pills may not work properly when taken while barbiturates are being taken. To prevent pregnancy, use additional or additional methods of birth control while taking barbiturates^[77].

Barbiturates may also interact with other medicines such as^[77]:

- Other central nervous system (CNS) depressants such as medicine for allergies, colds, hay fever, and asthma; sedatives; tranquilizers; prescription pain medicine; muscle relaxants; medicine for seizures; sleep aids; barbiturates; and anaesthetics.
- Blood thinners.
- Adrenocorticoids (cortisone-like medicines).
- Antiseizure medicines such as valproic acid and carbamazepine.

Azapirone

Azapirones, also known as azaspirodecanediones, are a class of psychoactive drugs derived from piperazine that are used as anxiolytics, antidepressants, and antipsychotics^[82]. They can be used on their own, or along with another drug (such as an antidepressant). The most commonly used AZP is buspirone^[83, 84]. Pharmacologically, they are primarily 5-HT_{1A} receptor partial agonists, and some are also prominent D₂, α_1 -adrenergic, α_2 -adrenergic, and/or 5-HT_{2A} receptor antagonists^[82].

List of Azapirones^[82]:

The Azapirones include the following agent:

1. Alnespirone
2. Binospirone
3. Buspirone
4. Enilospirone
5. Eptapirone
6. Gepirone
7. Ipsapirone
8. Revospirone
9. Tandospirone
10. Zalospirone

Pharmacokinetics

Azapirones have a rapid onset of action, but have only very short half-lives ranging from 1-3 hours. As a result, they must be administered 2-3 times a day. The only exception to this rule is umespirone, which has a very long duration with a single dose lasting as long as 23 hours^[85]. Metabolism of azapirones occurs in the liver and they are excreted in urine and feces. A common metabolite of several azapirones including buspirone, gepirone, ipsapirone, revospirone, and tandospirone is 1-(2-pyrimidinyl)piperazine (1-PP)^[86,87,88]. 1-PP possesses 5-HT_{1A} partial agonist and α_2 -adrenergic antagonist actions and likely contributes overall mostly to side effects^[86, 87, 89].

Side Effects

Dizziness, Headaches, Restlessness, Nausea and Diarrhoea. Unlike benzodiazepines, azapirones lack abuse potential and are not addictive, do not cause cognitive/memory impairment or sedation, and do not appear to induce appreciable tolerance or physical dependence^[90,91].

Hydroxyzine

Hydroxyzine is a first-generation antihistamine of the diphenylmethane and piperazine classes. It was first synthesized by Union Chimique Belge in 1956. Hydroxyzin acts as H₁ receptor antagonist and muscarinic acetylcholine receptor antagonist.

It is used primarily as an antihistamine for the treatment of itches and irritations, an antiemetic for the reduction of nausea, as a weak analgesic by itself and as an opioid potentiator, and as an anxiolytic for the treatment of anxiety. Even though it is an effective sedative, hypnotic, analgesic, and tranquilizer, it shares almost none of the abuse, dependence, addiction, and toxicity potential of other drugs used for the same range of therapeutic reasons.^[92]

Pharmacokinetics

Hydroxyzine is rapidly absorbed and distributed in oral and intramuscular administration, and is metabolised in the liver; the main metabolite through oxidation of the alcohol moiety to a carboxylic acid and overall effects are observed within one hour of administration. It has a half-life observed on average of around 7–10 hours in adults, 6–7 hours in children, and 18–21 hours in the elderly, or those with renal insufficiency, with higher concentrations found in the skin than in the plasma. Hydroxyzine and its metabolites are excreted in faeces via biliary elimination^[92].

Contraindications:

The administration of hydroxyzine in large amounts by ingestion or intramuscular administration during the onset of pregnancy can cause foetal abnormalities. Other contraindications include the administration of hydroxyzine alongside depressants and other compounds which affect the central nervous system^[93].

Adverse Reactions:

Deep sleep, in coordination and dizziness has been reported in children and adults, as well as others such as hypotension, tinnitus, and headaches. Gastro-intestinal effects have also been observed, as well as less serious effects such as dryness of the mouth and constipation caused by antimuscarinic properties of hydroxyzine. Central nervous system problems such as hallucinations or confusion have been observed in rare cases, attributed mostly to overdosage. In addition, many have reported abnormal weight gain and intense carbohydrate cravings after long term use of Hydroxyzine. Some users may report erectile dysfunction, shortness of breath or wheezing, a result of a mild allergic reaction to the medication itself^[94, 95].

PREGABALIN

Pregabalin is chemically related to gabapentin. It is used for treating pain caused by neurologic diseases such as postherpetic neuralgia as well as seizures^[96]. It also is used for treating fibromyalgia^[97] and spinal cord injury^[98]. It is also used to treat pain caused by nerve damage in people with diabetes (diabetic neuropathy). It has also been found effective for generalized anxiety disorder^[96].

Mechanism of action:

Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA) and has anxiolytic, analgesic, and antiepileptic properties. Pregabalin is structurally related to gabapentin. Pregabalin does not show direct GABA-mimetic effects, but increases neuronal GABA levels as well as produces a dose-dependent increase in glutamic acid decarboxylase activity. Pregabalin reduces neuronal calcium currents by binding to the alpha-2-delta subunit of calcium channels, and this particular mechanism may be responsible for effects in neuropathic pain, anxiety, and other pain syndromes^[99]. Glutamic acid decarboxylase (GAD) is the enzyme that converts the excitatory neurotransmitter glutamate into the inhibitory GABA in a single step. For this reason, pregabalin greatly potentiates benzodiazepines, barbiturates & other depressants. Pregabalin does not bind directly to GABA_A, GABA_B, or benzodiazepine receptors, does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake^[96].

Pharmacokinetics

1. **Absorption:** Pregabalin is rapidly absorbed when administered on an empty stomach, with peak plasma concentrations occurring within one hour. The rate of pregabalin absorption is decreased when given with food^[100].
2. **Distribution:** Pregabalin has been shown to cross the blood-brain barrier. The volume of distribution of pregabalin for an orally administered dose is approximately 0.56 L/kg and is not bound to plasma proteins^[100].
3. **Metabolism:** Pregabalin undergoes negligible metabolism in humans^[101]. Approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methyl pregabalin is the major metabolite^[100].
4. **Excretion:** Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug^[100].

Drug Interactions

Pregabalin is synergistic with opioids in lower doses, benzodiazepines, barbiturates, ethanol (alcohol), and other drugs that depress the central nervous system. Pioglitazone and rosiglitazone cause weight gain, fluid retention and possibly heart failure. Therefore, combining pregabalin with these drugs may increase the occurrence of weight gain and fluid retention^[102].

Uses: Pregabalin is indicated for:

1. Treatment of neuropathic pain from diabetic neuropathy or post herpetic neuralgia^[103,104,105].
2. Adjunctive therapy in adults with partial seizures with or without secondary generalization^[106,107,108].
3. Fibromyalgia^[97].
4. Generalized anxiety disorder^[109,110].

Adverse effects

Adverse drug reactions associated with the use of pregabalin include: Dizziness, Drowsiness, Visual disturbance (including blurred vision, diplopia), ataxia, dysarthria, tremor, lethargy, memory impairment, euphoria, constipation, dry mouth, peripheral edema, loss or decrease of libido, erectile dysfunction, weight gain, Depression, confusion, agitation, hallucinations, myoclonus, hypoesthesia, hyperaesthesia, tachycardia, excessive salivation, sweating, flushing, rash, muscle cramp, myalgia, arthralgia, urinary incontinence, dysuria, thrombocytopenia, kidney calculus, Neutropenia, first degree heart block, hypotension, hypertension, pancreatitis, dysphagia, oliguria, rhabdomyolysis, suicidal thoughts or behaviour. Pregabalin may also cause withdrawal effects after long-term use if discontinued abruptly. Withdrawal symptoms include restlessness, insomnia, and anxiety^[109,111].

Herbal treatments

Certain herbs are reputed to have anxiolytic properties, including the following:

1. *Aloysia polystachya*- The hydroalcoholic extract of *Aloysia polystachya* has been used for treatment of anxiety^[112].
2. *Apocynum venetum*- The ethanolic extract of the leaves of *Apocynum venetum* have been used in the treatment of anxiety^[113].
3. *Ginkgo biloba*- The aqueous extract obtained from the whole plant of *Ginkgo biloba* shows antianxiety activity^[114].
4. *Erythrina velutina*- The aqueous and alcoholic extract of *Erythrina velutina* possesses anxiolytic activity^[115].
5. *Magnolia dealbata*- The ethanolic extract of leaves of *Magnolia dealbata* have been used in the treatment of anxiety^[116].
6. *Turnera aphrodisiaca* - *Turnera aphrodisiaca* Ward (Turneraceae) has been used for treatment of anxiety neurosis and as an aphrodisiac^[117,118].
7. *Nepeta cataria*- With mild effectiveness for anxiety and insomnia, it may also have limited ability to treat migraines^[119].
8. *Valeriana species*- Valeriana species such as *V. walliichii*, *V. officinalis*, *V. eduli*, *V. thalictroides* have demonstrated anti-anxiety effect by a facilitation of GABA transmission^[120]. In vitro valerianic acid components have been shown to decrease the degradation of gamma-amino butyric acid (GABA)^[121].
9. *Tilia americana* L. Var. *Mexicana*- Methanolic extract of *Tilia americana* L. Var. *Mexicana* possesses sedative and anxiolytic activity^[122].
10. *Uncaria rhynchophylla*- The aqueous extract of hooks with stem of *Uncaria rhynchophylla* have been used in the treatment of anxiety^[123].
11. *Coriandrum sativum*- Aqueous extract of *Coriandrum sativum* seed has anxiolytic effect and may have potential sedative and muscle relaxant effects^[124].

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