Review Article

A Comprehensive Study on Anxiety: A Review

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ABSTRACT
Anxiety is the common disorder in the world. The persistence of anxiety is associated with significant personal distress, reduced quality of life, increased morbidity and mortality, and a substantial economic burden. Therefore these disorders are common in primary and secondary medical health care system. This present article is design to bring together the classes of anxiety, various pharmacological models used to evaluate anxiety disorder and treatment of anxiety with special emphasis on herbal drugs based on their traditional values.

Keywords: Anxiety, pharmacological models, herbal drugs.

INTRODCUTION

Anxiety is the common disorder in the community, and these are common in primary and secondary medical health care system [1]. Anxiety is a generalized mood condition that occurs without an identifiable triggering stimulus. As such, it is distinguished from fear, which occurs in the presence of an observed threat [2]. Normal anxiety may be defined as "a diffuse, unpleasant, vague sense of apprehension, often accompanied by autonomic symptoms - such as headaches, palpitations, tightness in the chest, restlessness, mild stomach discomfort that can be an appropriate response to a threatening situation or stimulus"[3]. Whereas fear is considered specific and targeted, anxiety is considered more diffuse and unfocused[4]. The disorders typically persist for many years, and are associated with significant personal distress, reduced quality of life, increased morbidity and mortality, and a substantial economic burden [5]. In interaction with cognitive parameters, anxiety regulates behavior in humans and other animals. The assessment of anxiety-related behavior in animal models is based on the assumption that anxiety in animals is comparable to anxiety in humans. As a matter of fact, it cannot be proved that rodents, the prime species in basic research, experience anxiety in the same way as human beings. However, it is undisputed that distinct behavioural and physiological patterns in rodents indicate anxiety, i.e., behavioural and peripheral changes presumed to accompany high sympathetic nervous activity[6].

Prevalence

Anxiety disorders are the most common type of Psychiatric disorders. The 1 year prevalence rate of anxiety disorders was 13.3% in person aged 18 to 54 years and 10.6% in those over age 55 years. Life time prevalence is 28.8%[7,8].

- Prevalence rate of generalized disorder for 1 year is 2.8%. It is more common in women (2%) than man (1%)[7].
- Panic disorder, with or without agarophobia has a life time prevalence rate of 2 to 4% [8]. It is about twice as common among women as men[2].
- The 1 year prevalence rate of social anxiety disorder is 3.7%[7] .
- The 1 year prevalence rate of PSTD is 3.6%[7]. It is more common in women (20%) than men (8.2%)[9].
- The 1 year prevalence rate for obsessive compulsive disorder is 2.4% in person aged 1 to 54 years and 1.5%

in those over age 55 years[7]. Life time prevalence is 2.3%[8].

Symptoms

Anxiety can be accompanied by physical 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. Anxiety does not only consist of physical symptoms. There are many emotional symptoms involved as well. Some of them include: "Feelings of apprehension or dread, trouble concentrating, feeling tense or jumpy, anticipating the worst, irritability, restlessness, watching (and waiting) for signs (and occurrences) or danger, and, feeling like your mind's gone blank."[10].

Types of anxiety disorders

The Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM-IV, 1994) classifies anxiety disorders in following categories. The characteristic feature of these illness are anxiety and avoidance behaviour.

Generalised anxiety disorder

The essential feature of GAD is excessive worry and tension about a number of events or activity without panic and phobic symptoms [7] [11].Other symptoms may include restlessness, fatigue, difficulty concentrating, muscle tension and sleep disturbance. GAD diagnosis is confirmed when an individual experience excessive worrying about number of events and three or more of the above symptoms more needs than not for least six months[4].

Panic disorder

Panic disorder begins as a series of spontaneous panic attacks, involving an intense, terrifying fear, similar to that caused by life threatening danger [7] [12]. Symptoms may include palpitation, sweat, trembling, feeling of choking, chest pain dizziness, chills or hot flashes.

Disorder is diagnosed when a person experience recurrent expected panic attacks and at least four of the following symptoms developed abruptly and reached a peak within 10 minutes; persistent concern about future attack, fear of dying, worry about the implication of attack and a significant change in behaviour related to the attacks[4].

Phobia

Social phobia

It is characterized by a fear of social or performance situations in which the person is exposed to position scrutiny by others. Principal physical indicator is blushing other symptoms are. Embarrassment feared situation in addressing a group of people, speaking in public, eating or writing in front of others. Physical symptoms are diarrhea, blushing, sweating, tachycardia, trembling[4,13].

Specific phobia

It involves excessive fear in response to a specific object or situation (e.g. insects, heights, blood or public transportation). Apart from contact with the feared object or situation, the patient is usually free of symptoms.

Obsessive-compulsive disorder

It is characterized by recurrent and persistent thought and repetitive ritualistic activities and behavior.A compulsion is a repetitive, purposeful, intentional behaviour or mental act usually performed in response to an obsession. (e.g. hand washing, checking, ordering, counting, repeating words silently praying)[4].

Post traumatic stress disorder

This occurs by experiencing or witnessing a traumatic or terrifying life event (e.g. serious accident, violent crime, symptoms include inability to sleep, hypersensitivity to external stimuli, loss of memory of time surrounding the traumatic experience).A diagnosis of PSTD also consider when a patient persistently re-experience the traumatic event by dreaming about it, experiencing hallucination or flash backs. For diagnosis, symptoms must be present for more than one month but may occur years after traumatic event[14,4,7].

Animal models

An animal model is a living, non-human animal used during the research and investigation of human disease, for the purpose of better understanding the disease without the added risk of causing harm to an actual human being during the process. The animal chosen will usually meet a determined taxonomic equivalency to humans, so as to react to disease or its treatment in a way that resembles human physiology as needed. Many drugs, treatments and cures for human diseases have been developed with the use of animal models[15,16]. Models representing specific taxonomic groups in the research and study of developmental processes are also referred to as model organisms [16].

Although humans and animals (technically "non-human animals") may look different, at a physiological and anatomical level they are remarkably similar. Animals, from mice to monkeys, have the same organs (heart, lungs, brain etc.) and organ systems (respiratory, cardiovascular, nervous systems etc.) which perform the same functions in pretty much the same way. The similarity means that nearly 90% of the veterinary medicines that are used to treat animals are the same as, or very similar to, those developed to treat human patients. There are minor differences, but these are far outweighed by the similarities. The differences can give important clues about diseases and how they might be treated. There are three main types of animal models Homologous, Isomorphic and predictive. Homologous animals have the same causes, symptoms and treatment options as would humans who have the same disease. Isomorphic animals share the same symptoms and treatments. This is the principle research tool. Predictive models are when the animals strictly display only the treatment characteristics of a disease. This method is commonly used when researchers do not know the cause of a disease.

There are various animal models that are being used for the research purposes. Following figure 1 and table 1 has shown the commonly used animal models for the screening anxiolytic activity.

Treatment of anxiety

Anxiety can be treated medically, with psychological counseling, or independently. Ultimately, the treatment path depends on the cause of the anxiety and the patient's preferences. Often treatments will consist of a combination of psychotherapy, behavioral therapy, and medications (Figure 2)[39].

Sometimes alcoholism, depression, or other coexisting conditions have such a strong effect on the individual that treating the anxiety disorder must wait until the coexisting conditions are brought under control.

Herbal treatment

Common limitations of anxiety drug therapy include co-morbid psychiatric disorders and increase in dose leading to intolerable side-effects [40]. It has led scientists to investigate plants which are commonly employed in traditional and alternative systems of medicine for sleep disorders and related diseases[41].A few plants that have been investigated for their anxiolytic effects include the following table 2: -

CONCLUSION

Traditional Medicines derived from medicinal plants are used by about 60% of the world's population. This review focuses on to identify the phytoconstituents which responsible for the treatment of anxiety disorder (which include generalized anxiety disorder, panic disorder, posttraumatic stress disorder and obsessive compulsive disorder). Although synthetic drugs are available but it has enormous adverse effects, so use of the herbs to treat anxiety disorder with having very few or no side effects. So that natural remedies are becoming the most popular alternative medication for the treatment of anxiety disorders. Now a days, research is carried out in the way to get new molecule and lead to deliver a good quality health care.

Table 1: List of different *in vitro* models used for Anxiolytic Activity

S. No.	Animal Model	Animal used	Principle
1.	Light and Dark Model	Rats and mice	This describes a simple behavior model in mice to detect compounds with anxiolytic effects. Mice and rats tend to explore a novel environment, but to retreat from the aversive properties of a brightly-lit open field[17].
2	Anticipatory Anxiety in Mice	Mice	When group-housed mice are removed one by one from their home cage, the last mice removed have always higher rectal temperatures than those removed first [18] [19]. This phenomenon is interpreted as being caused by anticipatory fear for an aversive event (handling causes stress-induced hyperthermia).
3	Social Interaction in Rats	Rats	In an unfamiliar and brightly lit environment, the normal social interaction of rats (e. g. sniffing, nipping, grooming) is suppressed. Anxiolytics counteract this suppression[20].
4	Elevated Plus Maze Test	Rats and Mice	The test has been proposed for selective identification of anxiolytic and anxiogenic drugs. Anxiolytic compounds, by decreasing anxiety, increase the open arm exploration time; anxiogenic compounds have the opposite effect[21,22,23].
5	Water Maze Test	Rats	Spatial learning of rats can be tested in a water maze[24,25].
6	Staircase Test	Mice	In the staircase paradigm, step-climbing is purported to reflect exploratory or locomotor activity, while rearing behavior is an index of anxiety state. The number of rearings and steps climbed are recorded in a 5min period [26].
7	Cork Gnawing Test in the Rat	Rats	Cork gnawing behavior in the rat has been proposed as a screening method for buspirone-like anxiolytics[27].
8	Distress Vocalization in Rat Pups	Rat pups	Measurement of ultrasonic vocalization induced by tail-holding in rat pups was proposed as a simple screening method for anxiolytic drugs[28].
9	Schedule Induced Polydipsia in Rats	Rats	Food deprived rats exposed to a procedure in which food is delivered intermittently will drink large amounts of water if given the opportunity to do so. This behavioral phenomenon is termed schedule-induced polydipsia and is an example of a more general class of behaviors termed adjunctive behaviors[29,30].
10	Four Plate Test in Mice	Mice	The four plate test in mice has been described for the rapid screening of minor tranquilizers [31,32].
11	Foot-shock-Induced Freezing Behavior in Rats	Rats	Footshock-induced freezing behavior in rats has been proposed as a model for anxiolytics [33]. Duration of foot-shock induced freezing after the second shock is taken as the critical parameter. Time spent in freezing posture after administration of test compounds is compared with the controls. Anxiolytics like diazepam and buspirone show dose-dependent effects, but not haloperidol.
12	Acoustic Startle Response in Rats	Rats	The acoustic startle reflex is a relatively simple behavior that occurs naturally in mammals and is affected by a variety of treatments. It consists of a series of rapid movements beginning at the head and moving caudally involving contraction and extension of major muscle groups in response to auditory stimuli with a rapid onset, or rise time [34].
13	Vogel Test	Rats	Vogel test is a simple and reliable conflict procedure for testing anti-anxiety agents. Thirsty, naive rats were administered shocks while licking water[35].
14	Novelty-Suppressed Feeding	Rats	Placing a hungry rat into an unfamiliar environment with access to food results in a suppression of feeding behavior relative to the condition when the test environment is familiar. This effect has been termed hyponeophagia and occurs because of the novelty of the test environment[36]. The avoidance of novel foods is termed food neophobia.
15	Shock Probe Conflict Procedure	Rats	Rats being placed in a novel test environment containing a probe, explore the environment and also the probe. The exploration of the probe, quantified as the number of times that the animal makes physical contact with it, is reduced when the probe is electrified. Rats treated with anxiolytics continue to touch the electrified probe[37].
16	Ultrasound Induced Defensive Behavior in Rats	Rats	Rats exposed to aversive stimuli display specific defence behavior as a part of their natural survival strategy. One component of this behavior is the production of ultrasonic calls in the 20–27kHz range, which are thought to serve a communication role. Artificially generated ultrasound produces intensity-related locomotion, characteristic of defensive behavior[38].

Table 2: Plant having anxiolytic activity

S. No.	Plant Name	Part Used	Extract	Dose	Reference
1	*Abies pindrow* Royle Pinaceae	Leaf	Ethanolic	50-100 mg/kg, p.o.	[42]
2	*Achillea millefolium* Linn. Asteraceae	Flower	Aqueous	8.0, 10.0, 12.0 mg/kg	[43]
3	*Aloysia polystachya* (Griseb.) Moldenke (Verbenaceae)	Leaf	Hydroalcoholic	1.56-50 mg/kg	[44]
4	*Albizia lebbeck* Benth. (Mimosaceae)	Leaf	Butanolic	25 mg/kg	[45]
5	*Albizia julibrissin* Durazz. (Fabaceae)	Stem bark	Aqueous	100 & 200 mg/kg	[46]
6	*Angelica sinensis* (Oliv.) (Apiaceae)	Root	Essential oil	30.0 mg/kg	[47]
7	*Aniba riparia* (Nees) Mez (Lauraceae)	Unriped fruit	riparin III	25 & 50 mg/kg	[48] [49]
8	*Annona cherimola* Mill. (Annonaceae)	Leaf	Hexane	6.25, 12.5, 25.0 and 50.0 mg/kg	[50]
9	*Apocynum venetum* Linn. (Apocynaceae)	Root	Ethanolic	30 and 125 mg/kg	[51]
10	*Azadirachta indica* A.Juss. (Meliaceae)	Leaf	Aqueous	10-200 mg/kg	[52] [53]
11	*Bacopa monnieri* (Linn.) Penn. (Scrophulariaceae)	Whole plant	Bacoside A	5, 10 and 20 mg/kg	[54]
12	*Casimiroa edulis* Llave & Lex. (Rutaceae)	Leaf	Aqueous	25 mg/kg	[55]
13	*Cecropia glazioui* Sneth (Moraceae)	Leaf	Aqueous & n-butanolic	0.25-1 g/kg	[56]
14	*Citrus sinensis* (Linn.) Osbeck (Rutaceae)	Peel	Essential oil	1 g/kg	[57]
15	*Clitoria ternatea* Linn. (Fabaceae)	Whole plant	Methanolic	----	[58]
16	*Coriandrum sativum* Linn. (Apiaceae)	Fruit	Aqueous	100 mg/kg	[59]
17	*Coptis chinensis* Franch (Ranunculaceae)	Rhizomes	berberine	100 , 500 mg/kg	[60]
18	*Crinum giganteum* Andrews (Amaryllidaceae)	Rhizomes	Aqueous	6.25, 12.5 and 25 mg/kg	[61]
19	*Davilla rugosa* Poir. (Dilleniaceae)	Stem	Hydroalcoholic	15 mg/kg	[62]
20	*Echium amoenum* Fisch.&C.A.Mey. (Boraginaceae)	Flower	Ethanolic	50 mg/kg	[63]
21	*Erythrina velutina* Willd. (Fabaceae)	Stem bark	Alcoholic	50-100 mg/kg	[64]
22	*Erythrina mulungu* Mart. Ex Benth. (Fabaceae)	Inflorescence	water-alcohol extract	50, 100, 200 mg/kg	[65]
23	*Eschscholzia californica* Cham. (Papaveraceae)	Inflorescence	aqueous alcohol extract	50, 100, 200 mg/kg	[66]
24	*Euphoria longana* Lam.(Sapindaceae)	Whole plant	adenosine	2 g/kg	[67]
25	*Euphorbia hirta* Linn. (Euphorbiaceae)	whole dried plant	Lyophilised aqueous	12.5 and 25 mg/kg	[68]
26	*Eurycoma longifolia* Jack (Simaroubaceae)	Root	Methanol, chloroform, water and n- butanol	0.3g/kg each	[69]
27	*Euphorbia neriifolia* Linn. (Euphorbiaceae)	Leaf	Hydroalcoholic	400 mg/kg	[70]
28	*Galphimia glauca* Cav. (Malpighiaceae)	Dried leaves	Methanolic	15 mg/kg	[71]
29	*Gastrodia elata* Blume (Orchidaceae)	Rhizomes	aqueous extract	50, 100, 200, 400 mg/kg,	[72]
30	*Ginkgo biloba* Linn. (Ginkgoaceae)	Whole plant	ginkgolide-A,	0.063-1 g/kg	[73]
31	*Hypericum perforatum* Linn. (Hypericaceae)	Whole plant	50% ethanolic extract	100-200 mg/kg	[74]
32	*Justicia hyssopifolia* Linn. (Acanthaceae)	Whole plant	Elenoside	25, 50 mg/kg	[75]
33	*Kielmeyera coriacea* Mart. Ex Saddi (Guttiferae)	Leaf	Hydroalcoholic	25 mg/kg	[76]
34	*Magnolia dealbata* Zucc.	Whole plant	Crude extract	30, 100 and 300	[77]

	(Magnoliaceae)			mg/kg	
35	*Pachyrrhizus erosus* (Linn.)Urban (Fabaceae)	Seed	Ethanol	150 mg/kg	[78]
36	*Paeonia moutan* Sims. (Paeoniaceae)	Root bark	paeonol	17.5 mg/kg	[79]
37	*Panax ginseng* C. A. Mey. (Araliaceae)	Root	ginsenoside Rb1	2.5, 5 and 10 mg/kg	[80]
38	*Passiflora incarnata* Linn. (Passifloraceae)	Leaves, Stems and flowers	Methanol		[81]
39	*Piper methysticum* G. Forst. (Piperaceae)	Roots	LI 150	120-240 mg/kg	[82]
40	*Rubus brasiliensis* Marit. (Rosaceae)	Whole plant	Ethanolic	150 mg/kg,	[83] [84]
41	*Salvia elegans* Vahl (Lamiaceae)	leaves and flowers	Hydroalcoholic	12.5 mg/kg	[85]
42	*Salvia reuterana* Boiss. (Lamiaceae)	Whole plant	Hydroalcoholic	100 mg/kg	[86]
43	*Salvia officinalis* Linn. (Lamiaceae)	Dried leaves	Ethanolic extract	300 mg and 600 mg	[87]
44	*Scutellaria baicalensis* Georgi (Lamiaceae)	Sage leaves	Wogonin	7.5 to 30 mg/kg	[88]
45	*Scutellaria lateriflora* Linn. (Lamiaceae)	Leaves	Ethanolic	1.6 mg/kg , 33 mg/kg and 40 mg/kg	[89]
46	*Sesbania grandiflora* Pers. (Fabaceae)	Leaves	Benzene : ethyl acetate fraction of acetone	100 mg/kg	[90]
48	*Sphaeranthus indicus* Linn. (*Asteraceae*)	Flowers	Petroleum Ether	10 mg/kg	[91]
49	*Stachys lavandulifolia* Vahl. (Lamiaceae)	aerial parts	Hydroalcohol Extract	50 mg/kg	[92]
50	*Tragia involucrata* Linn. (Euphorbiaceae)	Root	Methanolic	30, 100 and 300 mg/kg	[93]
51	*Turnera aphrodisiaca* Ward. (Turneraceae)	Dried mother tinctures	Mother tinctures (85% ethanol extracts)	50, 75, 125 mg/kg	[94]
52	*Uncaria rhynchophylla* (Miq.) Jacks (Rubiaceae)	hooks with stem	Aqueous	100-200 mg/kg	[95]
53	*Valeriana edulis* ssp. *procera* Mey. (Valerianaceae)	Root	Hydroalcoholic	100, 300 and 1000 mg/kg	[96]
54	*Withania somnifera* (Linn.) Dunal (Solanaceae)	Root	glycowithanolides	20 and 50 mg/kg	[97]
55	*Zingiber officinale* Rosc. (Zingiberaceae)	dried rhizomes	petroleum ether extract	100, 200 mg/kg	[98]
56	*Ziziphus jujube* Mill. (*Rhamnaceae*)	Pulp	Ethanolic	0.5-2.0 g/kg	[99]

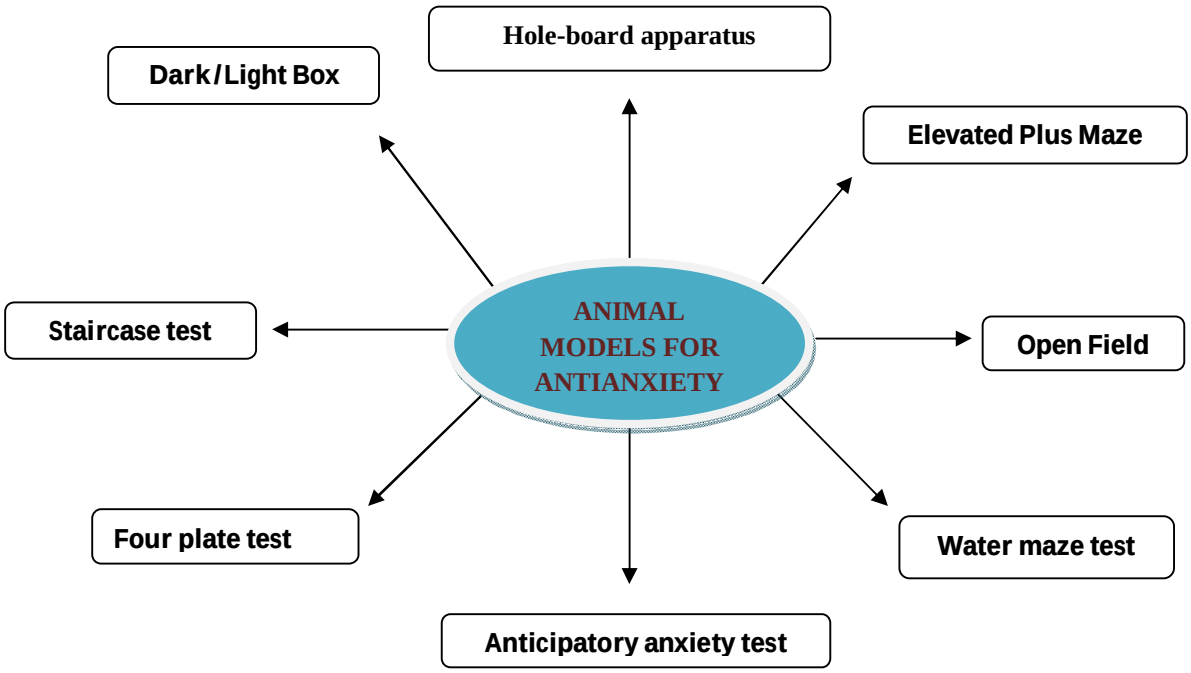

Fig. 1: Animal models for anxiolytic activity

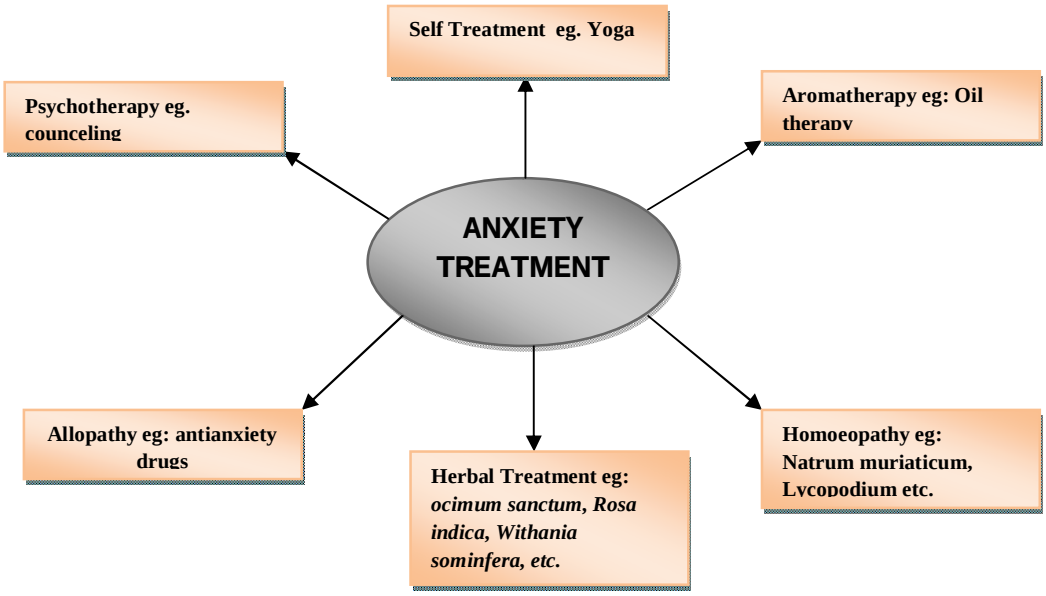

Fig. 2: Various treatments of anxiety disorder

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