Etiology and Treatment of Anxiety

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Abstract. There is still much debate about the etiology and remedies of anxiety disorders. Summarizing the current research results will facilitate a deeper understanding of anxiety disorders and uncover suitable treatments. Environmental changes, childhood trauma or physical abuse, and a Mediterranean diet or the microbiome were strongly associated with disease development. Also, the PDE4B gene, other essential loci, and 274 genes' interaction with the environment could potentially cause anxiety. Molecules such as the brain receptor GPR158, MicroRNA-137, and the interleukin-17a (IL-17a) showed increased anxiety behaviors. Psychological therapy, such as cognitive behavioral treatment, mindfulness-based cognitive therapy, and internet-delivered behavioral therapy, effectively reduces anxiety. Diazepam and clonazepam, secondary benzodiazepine treatments, showed shortcomings, for example, the former lack of cognitive recovery. Furthermore, SSRIs, including sertraline, fluoxetine, and paroxetine, and SNRIs like venlafaxine or duloxetine, had good efficacy and high tolerability. Animal-assisted intervention, cannabidiol, molecule therapeutics, and many novel approaches in different systems were also proved to be beneficial in decreasing anxiety symptoms. More evidence from studies and reviews is needed to support these findings.

1. Introduction

Occasional anxiety is a normal stress response; therefore, it is a normal part of life. However, unmanageable worries or fears might signal the presence of neurological illnesses, which interfere with the patient's daily activities such as performance in job, school, and relationships.

One of the most frequent mental illnesses was anxiety disorder. The prevalence was between 2.4 percent to 29.8 percent, as analyzed by a team who did 87 research from 44 different nations [1]. Approximately 22.8 percent of individuals were judged to have a severe impairment, 33.7 percent to have a moderate impairment, and the majority to have a light impairment (43.5 percent), based on the National Comorbidity Survey replication results. Of the individuals with the disorder, females accounted for 63%, maybe because of their more significant hormone fluctuations. Moreover, The COVID-19 pandemic caused a 25% rise in the prevalence worldwide. According to the prospective cohort study, 1066 (2.1%) people with anxiety disorders died after an average follow-up of 9.7 years using data from the Danish national registry and more than 30 million person-years of follow-up [2]. Thus, this mental illness, affecting numerous people, needs extreme attention and effective treatments.

A few of the several forms of anxiety disorders are generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), and phobia-related conditions. Post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) have similar syndromes. These specific types of illnesses have comparable symptoms. GAD causes patients to be in constant uncontrollable apprehension or have unexplained body pains and sleeping problems. In addition, patients might suffer from irregular breathing, trembling, and sweating during a phobia-related disorder. While in panic disorder, patients might experience sudden panic attacks, a period of intense fear and discomfort even when no apparent triggers exist. Therefore, it is essential to have a deeper understanding of the causation and mechanisms and choose the most effective treatment for each type of anxiety disorder.

As detected by RS-fMRI, anxiety disorder resulted in changes in brain activity, for example, a decrease in the spontaneous regional activities occurring in the right putamen, the right orbital region of the inferior frontal gyrus, and the right temporal pole [3]. Among all three parts, the right putamen experienced the most severe decline, positively correlated with childhood maltreatment. Similarly, Indicating a decreased brain activity, the right orbital area of the inferior frontal gyrus had a lower cortical thickness, and the right temporal pole showed a difference in gray matter volume.

Anxiety disorder causes included genetics, neurological function disruptions, stress, or life experiences. A few of the genes that are involved in anxiety are 5-HTT, MAO-A, and COMT [4]. For instance, a patient with anxiety could have inherited a gene such as RBFOX1 because the genetic heritability is around 31.6%

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[5]. Furthermore, environmental factors, and traumatic experiences, including childhood sexual abuse and natural disasters, could trigger the condition. Moreover, the malfunction of sending neurons from sensory cortices, thalamus, ventromedial prefrontal cortex, and hippocampus to the amygdala might also play a role because the amygdala is involved in an instinctive fear reaction and the synthesis of emotion and memory. Additionally, extreme stress may lead to changes in serum levels of hormone imbalance, consequently causing anxiety. More research is needed to understand anxiety disorder's gene and environmental causes.

Psychotherapy and pharmacotherapy are frequently used as treatments for anxiety disorders. Those multimodal approaches may target specific symptoms, and psychotherapy could increase adherence and decrease the side effects of pharmacotherapy. One psychotherapy is cognitive-behavioral therapy (CBT), which is based on the relationships between cognition, emotion, and behavior. Many psychotherapists personalize and customize the CBT treatment to each patient's specific needs to modify the patient's patterns of thinking and behavior. On the other hand, pharmacotherapy also shows efficacy for GAD. The first-line medications that have efficacy for short-term and ongoing relapse prevention, safety, and tolerability include the serotonin-norepinephrine reuptake inhibitors (SNRIs: venlafaxine and duloxetine), as well as the selective serotonin reuptake inhibitors (SSRIs: paroxetine, sertraline, and escitalopram). Additionally, Benzodiazepines, buspirone, pregabalin, and tricyclic antidepressants are examples of second-line drugs. On top of that, other treatments include animal-assisted treatment and cannabidiol (CBD). With satisfactory treatment, patients of different ages and different types of anxiety could live carefree with reduced symptoms and concerns about the medications. Since those medications are crucial treatments for anxiety, more research is required to demonstrate the effectiveness and safety of each type of treatment.

To conclude, an anxiety disorder is one of the most widespread mental illnesses affecting countless individuals. Therefore, this review introduces the environmental, genetic, and environment and gene interaction that causes this disorder and evaluates the treatments such as psychotherapy, pharmacotherapy, and animal-assisted therapy.

2. Etiology of anxiety

2.1 Environmental Factor

2.1.1 Climate Change

Environmental changes, including a rise in the frequency of severe weather conditions, more gradual climatic changes, and increased pandemics risks, evoked either adaptive or maladaptive anxiety [6]. Hazardous weather stressors or recurrent events that entail the loss of property, possessions, and loved ones were associated with increased risk factors for anxiety-related pathology [7]. In addition, housing shortage, crowding in shelters, and inability to access medical care could also be potential stressors. Consequently, when people's actions were not enough to cope with the acute and chronic climate change stressors, their anxiety levels deteriorated.

Climate-related stressors significantly impacted younger people, climate lovers, and people in poverty or precarious circumstances. These climate-related anxieties needed three types of interventions: programs for mental health care that encourage people to overcome nervous passivity, deal with anxiety brought on by exposure to environmental stressors, and foster resilience in both individuals and communities.

2.1.2 Childhood Trauma

Childhood trauma was one of the risk variables for the development of anxiety (as shown in figure 1). In the Czech Republic, a representative sample of people and patients with clinically diagnosed anxiety reported anxiety, long-term pain, and childhood trauma in a cross-sectional study using questionnaires. [8]. The findings indicated that anxiety was linked to reporting emotional abuse and emotional and physical neglect. The prevalence of noting these types of childhood trauma was substantially higher in the community sample reporting anxiety and pain than in the community sample reporting no chronic conditions. Yet, compared to the three community populations, these traumatic experiences were much more common in the clinical sample.

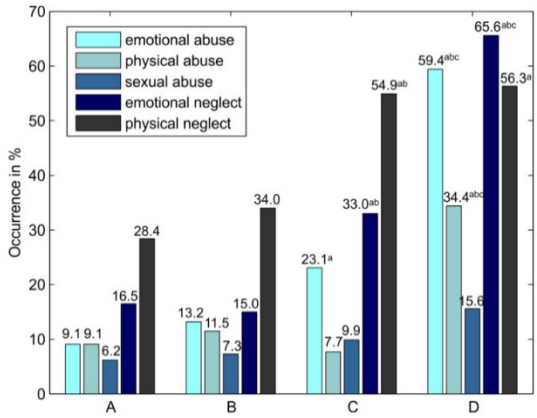

Figure 1: The frequency of different forms of childhood trauma in the research groups. (A) In the community group, where there was no chronic illness. (n = 405); (B) In the community group, where there was other chronic illness (n = 506); (C) In the community group, where there was anxiety and pain (n = 91); (D) Clinical group(n = 32) [8].

Furthermore, a review of all studies from the NESDA cohort containing childhood trauma findings related to psychopathology from 2009 to 2020 showed a correlation between childhood trauma and the higher risk, the onset, the recurrence, and the poorer comorbid and chronic outcomes of anxiety disorder. Moreover, childhood trauma was associated with brain alterations, for example, reduced medial prefrontal cortex (mPFC) volume and increased amygdala reactivity [9]. The mPFC is an essential cortical region that plays a role in the capacity to

control one's emotions, drive, and sociability. Therefore, mPFC impairment was linked to several neurological conditions, including anxiety [10]

Patients should be examined for signs of childhood trauma to receive adequate treatment methods planning [8]. More awareness of these factors could benefit primary and secondary prevention in public health and treatment programs for patients with anxiety.

2.1.3Diet and Micro-biota

Research proved that the microbiota was connected to the brain bidirectional relation, or the microbiome-gut-brain axis, which regulated brain activity and behavior in an essential way. Individuals with inflammatory bowel disease and irritable bowel syndrome had high anxiety comorbidity. Besides, in examining the association between the Mediterranean Diet Score (MDS)'s individual food groups with anxiety and depression, the result showed MDS score expressed the most vital relationship with anxiety [11]. For example, a higher intake of non-refined veggies and grains was associated with reduced anxiety severity. The severity of the anxiety was shown to be lessened by eating more fruits and vegetables.

2.2 Genetic Factors

Anxiety Disorder's liability scale common variant heritability was estimated to be 26 percent, and the Current Anxiety Symptoms are 31 percent. The genome-wide association study showed five novel loci relating to anxiety, including an intergenic region on chromosome 5 and chromosome 9 that was associated with neuroticism. Besides, a locus was found in NTRK2, the Brain-Derived Neurotrophic Factor (BDNF) receptor gene that regulates both short-term synaptic functions and long-term potentiation of brain synapses. On chromosome 7, the third locus was discovered in Transmembrane Protein 106B, a gene related to lysosomal enlargement and cell toxicity involved in depression. Lastly, the locus related to anxiety on chromosome 3 was a gene that produces a group of motor proteins that are prominently expressed in the brain. Neuroticism and anxiety traits were significantly associated with formal replication at two of the five loci.

In addition, the genome-wide association data studied associates variants in the PDE4B gene, which regulated intracellular cyclic adenosine monophosphate signaling, with anxiety and stress-related disorders [12]. The locus overlapped PDE4B with the lead SNP rs7528604; a framework of sensitivity analyses adjusting for mental comorbidity supports the result. The study sample involved 12655 individuals with anxiety and stress-related diagnoses and 19225 controls. Results showed a substantial role in typical genetic variation because the SNP heritability was 28%.

In the mouse model, after the mouse was exposed to prolonged stress in the hippocampus and prefrontal cortex, they showed anxiety-like behavior and changes in Pde4b expression. In tests susceptible to anxiolytic drugs, B6 mice sensitive to chronic psychosocial stress showed alteration in the expression of Pde4b compared to controls and stress-resilient mice. Lower expression levels in the brain region (mPFC and vHPC) regulated emotional and social behavior. Also, areas including the promoters and enhancers of expression in the tissues of the central nervous system and conserved regions had associations with anxiety disorder.

2.3 Gene and Environment Interaction

A gene-environment (G x E) interaction study showed how five features of perceived parenting interacted with 274 genes across nine neurotransmission systems (serotonin, dopamine, hypothalamic pituitary adrenal axis, oxytocin, GABA, glutamate, choline, noradrenergic, and clock pathway) as environmental exposure influenced social anxiety symptoms (SAS) in adolescence [13]. The focus of G x E studies was on the interaction effects of genetic variants and environmental factors, assuming that when people with susceptible genotypes were exposed to specific environmental conditions, their disease risk increased. The study's results demonstrated that the contribution of SAS was associated with harsh punitive (HP) parenting and its connection to genes related to glutathione neurotransmission (GSTZ1), glutamate (SLC1A1), and oxidative stress (CALCRL). In interaction with two significant genes, SLC1A1 and GSTZ1, there was only one parenting dimension (HP control). This study demonstrated that harsh parenting and polymorphisms in the GSTZ1 and SLC1A1 together contributed to the onset of social anxiety disorder.

2.4 Molecular and cellular mechanisms

2.4.1 Brain Receptor GPR158

The GPR158 was a brain-cell receptor highly expressed in the prefrontal cortex of people diagnosed with anxiety. This receptor was one of the key molecules because it was a critical regulator of behavioral responses to stress, a significant risk factor for major depressive disorders (MDD). Studies showed a strong correlation between the emotional state of the animal and the levels of GPR158. The mice exposed to physical restraint stress showed a considerable elevation in the levels of PR158 comparing to other orphan receptor candidates, which was supported by figure 2.

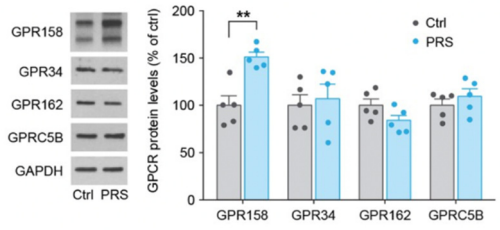

Figure 2: Representative western blots and protein level quantification of a selection of orphan receptors found in the mPFC of control non-stressed (Crtl) and mice subjected to chronic Physical Restraint Stress (PRS) (n = 4–5 mice/group; Student's t test; *p<0.05) [14].

Eliminating the level of GPR158 in chronically stressed mice promoted resiliency to anxiety-like behavior, while inducting GPR158 increased the effect of stress. Furthermore, humans with MDD have an uplifted GPR158 level compared to individuals without MDD. In short, an increase in GPR158 could be an etiology for the development of anxiety.

2.4.2 MicroRNA-137

MicroRNA was tiny and conserved non-coding RNA molecules. The researchers discovered that the miR-137 was essential for synaptic and dendritic development in the forebrain using a miR-137 knockout (cKO) mouse line. Removing the miR-137 in the nervous system of the mice exhibited anxiety-like behavior and diminished spatial learning and memory. In the open field experiment, the total distance the wild type (WT) and the mir-137 cKO mice moved during the half hour showed no significant difference, which was about 30 m. This result suggests the mice had similar locomotor activities. However, cKO mice only spent about 0.6% of their time in the central zone, but the WT spent about 2.0% of their time in the central area. Besides, the cKO mice only entered the central location five times, about half of the time WT mice did. Later, the researchers noticed the miR-137 knockout mice showed an uplifted expression of EZH2. They provided evidence that the knockdown of EZH2 can reduce anxious symptoms related to the miR-137 deficiency. To conclude, the results indicate that the deprivation of miR-137 contributes to anxiety, and EZH2 could be a possible therapeutic target for anxiety associated with malfunctioning miR-137. [15]

2.4.3 Immune System molecule IL-17a

The immune system not only destroys invading pathogens but may also contribute to anxiety in response to infection. The interleukin-17a (IL-17a) cytokines, or immune signalling molecule, could trigger anxiety-like symptoms in the mouse. The gamma-delta T cells that produce IL-17a were in the membranes surrounding the central nervous system. The researchers conducted tests on mice with different levels of delta T cells and IL-17 and gave the mice choice of entering exposed areas, which they feared due to the explosion of predators. The mice who did not have gamma-delta T cells or did not produce IL-17a explored the open spaces, indicating decreased anxiety. Contrastingly, the mice with an average level of IL-17 stayed in enclosed and protective edges, showing the presence of anxiety. Also, when the researcher removed the receptors on neurons that respond to IL-17 so that neurons could not detect the existence of IL-17, the mice showed less alertness and anxiety. [16]

3. Treatment

3.1 Psychological therapy

3.1.1 Cognitive Behavior therapy (CBT)

The common sense model of cognitive behavioral therapy emphasized the relationship between cognition, emotion, and action [17]. The behavior therapies reduced maladaptive behaviors and improved adaptive ones by changing their antecedents and consequences and performing actions that lead to new learning. In addition, the cognitive interventions would adjust abnormal cognitions, self-statements, and beliefs. CBT could be used alone to replace negative automatic thoughts in GAD or with medication like serotonin reuptake inhibitors.

The meta-analysis of the randomized clinical trials on post-treatment and several follow-up effects of CBT suggested that until 12 months after treatment, CBT for anxiety was related to improved outcomes compared with control conditions [18]. The follow-up of 12 months or more indicated that the effects are significant for PTSD, small to medium for GAD and SAD, and not available or essential for other anxiety-related disorders. In contrast to uncontrolled studies, which have a 23 percent recurrence rate for PD, the relapse rates following effective CBT were modest (0 percent to 14 percent). Another randomized controlled trial of CBT involving children younger than 19 years old, parents, or both in comparison with no treatment and other treatments for anxiety showed that CBT increased post-treatment remission of primary anxiety diagnoses [19].

Furthermore, a study of CBT's efficiency in declining the anxiety symptom of youth with OCD showed that CBT might bring a linear decrease in primary anxiety and benefit secondary anxiety symptoms [20]. Although there were changes in anxiety severity, these alternations were not related to specific improvements in OCD impairment or seriousness. Instead, it was linked to global ratings of treatment response. To conclude, CBT showed a long-term effect on PTSD, effectiveness in the short term in treating anxiety in adolescents, and a linear decrease in anxiety symptoms in youth with OCD.

3.1.2 Mindfulness-based cognitive therapy for GAD

Mindfulness-based cognitive therapy (MBCT) reduced GAD symptoms and anxiety sensitivity by minimizing the involvement in negative thoughts and feelings with a mental orientation by targeting exercises and awareness about living in the present time [21]. The MBCT allowed patients to pay attention to their body or physical and psychological sensations. A credible meta-analysis indicated that MBCT was an effective intervention for GAD. The result was reliable since there are 403 total samples, the effective sizes range from -0.017 to -1.07, and the effect was significant. In the MBCT, the overall risk ratio for GAD compared to controls was 0.65, and there was high methodological quality for the six studies.

3.1.3 Internet-delivered Cognitive Behavioural Therapy for GAD

Internet-delivered CBT (iCBT) was evidence-based psychotherapy performed using the internet. The iCBT was divided into two options, guided or unguided; guided iCBT involved communication with a regulated health care professional. A health technology assessment using iCBT to treat mild to moderate anxiety disorders comprised the therapeutic benefit, cost-effectiveness, patient preferences, and iCBT values [22]. The result suggested that compared with people on a waiting list, people who had undergone guided iCBT for mild to moderate anxiety, GAD, and social phobia showed a significant improvement in symptoms. After they received iCBT compared with people on a waiting list, there was considerable improvement in quality of life for people with GAD. Moreover, guided iCBT represents good value for money, and adults with mild to moderate major anxiety disorder could choose it as a short-term treatment. In addition, many people believe that iCBT provides greater control over time, pace, and location, despite some perceived limitations.

Besides, 103 youths who met the eligibility of SAD entered ten weeks of randomized therapist-guided iCBT (n=51) or therapist-guided internet-delivered supportive therapy (ISUPPORT), iCBT's active comparator [23]. The iCBT was more effective in decreasing SAD symptoms' severity than ISUPPORT. Furthermore, the cost-effectiveness analyses indicated that in the iCBT group, lower pharmaceutical expenses and greater academic output were the essential cost-saving factors. Therefore, Internet-delivered cognitive behavioral therapy was a valuable and affordable solution for kids and teenagers with SAD.

Finally, some meta-analyses compared the effects of iCBT for anxiety disorders with clinical results of trials with open recruitment trials (community recruitment) to the outcomes of clinical service recruiting studies (outpatient clinics recruitment) [24]. The higher effect size for the decrease in anxiety symptoms was expressed significantly in iCBT open recruitment studies with waitlist control comparators than the clinical recruitment. Accordingly, compared to patients with anxiety disorders receiving regular care, research participants chosen from the community might benefit more from iCBT.

3.2 Pharmacotherapy

The pharmacotherapy of anxiety disorder started with the early benzodiazepines (BZ) to selective serotonin reuptake inhibitors (SSRIs) and related substances, the serotonin and norepinephrine reuptake inhibitors (SNRIs). Specific medication reacted selectively to each form of anxiety illness [25].

3.2.1 Antidepressants

Two different types of antidepressants, SSRI and SNRI, that act on neurotransmitters like serotonin and norepinephrine, chemicals in the brain that move nerve messages across a cell synapse between neurons [26]. Two neurotransmitters that have different functions are excitatory neurotransmitters and inhibitory neurotransmitters. Serotonin neurotransmitter can carry out both roles; it aids the body in controlling mood. When the serotonin level drop, it could cause anxiety or obsessive-compulsive behaviors. In comparison, norepinephrine is only an excitatory neurotransmitter that plays a vital role in the fight-or-flight response, sleep, focus, memory, and emotional control. Therefore, when norepinephrine concentration fluctuates, a person could develop mental illness.

3.2.2 SSRI

The SSRIs prevented the reuptake of dopamine, serotonin (5-hydroxytryptamine, 5-HT), and norepinephrine [27]. The levels of synaptic 5-HT rose when 5-HT reuptake is suppressed, consequently enhancing extra-synaptic diffusion. Compared to norepinephrine and dopamine transporters, the SSRIs differed in terms of their efficacy and selectivity for the 5-HT transporter. Besides, these compounds had many adverse effects and varied efficacy characteristics because of their difference in their capacity to engage with extra-synaptic and synaptic receptors.

The first SSRI to be introduced in the United States was fluoxetine, which was created in the 1970s. Central serotonergic transmission, as well as noradrenergic and dopaminergic effects, are boosted by it. A study comprises the treatment with fluoxetine (FLX), Quality of Life and Psychoeducation (QoL), and Body in Mind Training (BMT) program for adults with GAD through a randomized clinical trial [28]. In week eight, the Hamilton The key outcomes were evaluated using the Anxiety Rating Scale (HAM-A) and the Penn State Worry Questionnaire (PSWQ). After the intervention, all three groups improved, but FLX was superior to the BMT by a small pre-specified amount as they were assessed with theHAM-A, and PSWQ scores [29]. Another study tested heart rate variability (HRV) to compare the MBI and fluoxetine treatment response. The HRV identified that fluoxetine was overall slightly superior to BMT, indicating that it is a more effective treatment method for anxiety disorder.

A sample of children and adolescents, who were 7-18 years old and had been treated with sertraline, was used in the naturalistic therapeutic drug monitoring research [30]. The findings demonstrated a linear, substantial positive association between sertraline serum levels and clinical effectiveness for pediatric OCD, as well as the importance of co-medication and weight. There was no correlation between dosage and serum concentration to any negative consequences. Furthermore, with a mild to moderate tolerance profile, sertraline might be tolerated by individuals.

In adult patients with social anxiety disorder, a thorough literature evaluation calculated paroxetine's effectiveness and tolerability [31]. In those patients who received paroxetine compared with those who received placebo, the former showed significantly more significant mean changes observed in the fear and avoidance

subscales of the Liebowitz Social Anxiety Scale (LSAS) scores and the total LSAS score. In addition, the rates of response and remission were also noticeably higher. Thus, paroxetine treatment for adult patients with SAD was effective and well-tolerated.

3.2.3 SNRI

The antidepressant SNRIs stop both serotonin and norepinephrine reuptake, the process through which the brain takes in neurotransmitters and makes them less available. Consequently, the reuptake inhibitors increase the availability so that SNRIs increase serotonin levels in the brain to reduce anxiety symptoms. Moreover, SNRIs could also increase norepinephrine levels, which helps the patient to concentrate and reduce depression symptoms [26].

The remission rate and tolerability of medications used to treat GAD were compared in a comprehensive review and network meta-analysis of double-blind, randomized controlled trials [32]. Among all drugs, the remission rate of venlafaxine was superior to placebo, more effective than tiagabine, and superior to vortioxetine. However, its tolerability, as measured by withdrawal owing to adverse events, was poorer than the placebo. In six current trials with 2,218 patients, an analysis of venlafaxine shows that its remission rate was considerable, and its tolerability was comparable to other drugs (referring to Table 1: the SUCRAs and mean ranks of drug ranking).

Table 1. The SUCRAs and Mean Ranks of Drug Ranking [31]

Outcomes	Treatments	SUCRA	Mean rank
Remission Rate	Agomelatine	89.7	2.1
	Venlafaxine	77.2	3.5
	Escitalopram	67.1	4.6
	Sertraline	64	5
	Duloxetine	57.6	5.7
	Quetiapine	58.6	5.9
	Paroxetine	49.2	6.6
	Pregabalin	46.3	6.9
	Lorazepam	41.2	7.5
	Vortioxetine	23.9	9.4
	Tiagabine	19	9.9
	Placebo	6.2	11.3
Tolerability	Sertraline	88.2	2.3
	Vortioxetine	85.6	2.6
	Agomelatine	82.9	2.9
	Placebo	79.8	3.2
	Pregabalin	57.2	5.7
	Escitalopram	52.3	6.2
	Tiagabine	46	6.9
	Duloxetine	35.2	8.1
	Paroxetine	30.7	8.6
	Venlafaxine	31.6	8.6
	Quetiapine	7.4	11.2
	Lorazepam	3.2	11.7

A systematic review including 85 studies that focus on the effectiveness, acceptability, and safety of duloxetine in treating anxiety symptoms evaluated 11 studies of GAD individually [33]. When measuring the effectiveness (90.9% studies), statistical significance, along with safety and tolerability (27.3% studies), were found. The most frequent AEs are nausea, dry mouth, dizziness, and drowsiness, according to the measure of TEAEs. Compared to placebo and venlafaxine, duloxetine was more efficient, secure, and well-tolerated.

3.3 Benzodiazepines

Benzodiazepines (BZ) were the oldest class of medication with the benefit of a quick start to action. However, they face the possibility of tolerance, sedation, and reliance. To affect the inhibitory neurotransmitter GABA and exert sedative effects, the BZ diffused through the blood-brain barrier. It was excellent for people who occasionally experience anxiety or insomnia [27].

One study observed the random distribution of 15mg/kg/day and the control group of 30 mg/kg/day of diazepam-supplemented pallets to 105 male C57B/6 mice [34]. After the mid-treatment test battery, the analysis indicated no age effect. The group receiving 15 diazepams had worse working memory than the control group. For the post-treatment assessment of cognitive abilities, three further improved tests did not show any differences between groups. Even though there was a cognitive impact during therapy, the fact that diazepam did not restore cognitive function after a lengthy course of treatment implies that it might have permanent negative consequences.

Following a protracted course of clonazepam therapy, a study focused on local in the rat brain, the stress-related neuropeptides- neuromedin U (NMU) and neuropeptide S

(NPS)- was expressed [35]. Due to chronic administration of clonazepam, there was a rise of NMU mRNA, and the amygdala depicts a formation of NMU-expressing fibers. Another study conducted trials to determine if etifoxine was non-inferior to clonazepam as a treatment for anxiety disorders [36]. The data shows that although clonazepam was effective, etifoxine shows non-inferiority to this active control treatment in reducing anxiety symptoms and presenting fewer side effects.

3.4 Animal Assisted therapy

To explore animal-assisted therapy's effects on individuals with anxiety disorders, 51 patients were separated into a treatment group that walked a dog for 15-20 minutes and a control group that walked with a researcher [37]. In comparison to the control group, the treatment group experienced much less anxiety and terror following the session. The data that support the finding came from the State-Trait Anxiety Inventory (STAI) technique, a questionnaire evaluating anxiety and its alterations, and a visual analogue scale (VAS) of anxiety that measured how satisfied participants were with the intervention. Participants in the treatment condition were also more satisfied with the intervention. According to the results, the treatment group experienced less anxiety as a whole and less terror than the control group. Walking without a dog only reduced state anxiety but walking with a dog significantly decreased state anxiety, resting heart rate, trait anxiety, and terror. To conclude, a dog's company was beneficial in reducing anxiety symptoms.

3.5 Potential drug targeted for anxiety disorder

Cannabidiol (CBD) was the most abundant non-psychoactive part of cannabis. Since it interacts with a range of brain molecular targets, it could be a potential treatment for anxiety and mood disorders. Especially, CBD became more frequently studied because it exhibited anxiolytic and antidepressant properties. In the study of CBD effects in animal models of anxiety using different mechanisms, 16 out of 18 models showed anxiolytic effects. Although the CBD's precise molecular mechanism of action was unknown, the researchers supported the use of CBD by performing animal-based studies. They also associate the neuropharmacological evidence of the molecular pharmacology of CBD with its behavioral effects. [38]

High levels of GPR148 were associated with increasing anxiety symptoms. The GPR148 was an orphan receptor because, unlike other receptors in its family, it had a tight association with the RGS (regulator of G protein signaling) protein complex. New studies proved that GPR158 bonded the RGS complex like other receptors engaged in their conventional transducers. Besides, the scientist found phospholipids were stabilizing the two halves of the GPR158 protein receptors. Lastly, the outside face of the receptor revealed the cache domain, which possibly captured the molecules that activated GPR158. Martemyanov, Professor and Chair of the Department of Neuroscience at Scripps Research, was exploring approaches to design molecule therapeutics to lower Anxiety symptoms. Some possible strategies were to disrupt the receptor structure, interfere with the involvement of the RGS complex, or use molecular binders to target the cache domain. [14]

Refining and enhancing substances that interact with already-existing anxiolytic therapeutic targets, such as serotonergic and archetypal GABAergic benzodiazepines, is one approach used in drug development. A more creative strategy entails exploiting the relevant neurocircuitries and neurobiological mechanisms underlying pathological fear and anxiety to seek for substances with unique mechanisms of anxiolytic effect. Compounds such as D-cycloserine (DCS), NYX-783, MDMA, and L-DOPA were also very effective in enhancing fear-extinction learning and decreasing anxiety disorders. Firstly, although it is not anxiolytic, the partial NMDA receptor agonist DCS could eliminate fear in rodents. Also, NYX-783, another NMDA receptor-activating molecule, increased synaptic plasticity and sped up extinction learning. In phase 1 human study, NYX-783 had shown high oral bioavailability and had been well tolerated. Secondly, the entactogen MDMA (3,4-methylenedioxymethamphetamine, ecstasy) also facilitated fear extinction in rodents and healthy humans. It increased central levels of 5-HT, Dopamine, and noradrenaline. MDMA had been used in the treatment of PTSD because it allowed the patient to cope with their trauma without undergoing fear during psychotherapeutic sessions. Lastly, the L-3, 4-dihydroxyphenylalanine (L-DOPA) facilitated fear disappearance and decreased fear relapse in humans because it promoted related neuronal plasticity in the IL and amygdala and encoded a reward-like signal. [39]

According to research, two strategies may aid in the creation of a medication by targeting central chemosensory and understanding of the connection between altered cytokine balance and interaction of cytokines and monoaminergic pathways. These approaches shared similar mechanisms of generating anxiolytics-like effect using pharmacological effects on acid-sensing ion channels. [40] In addition, the glutamate, endocannabinoid, voltage-gated ion channels, and the interrelation of oxytocin with neuropeptide S or vasopressin could also contribute to the development of new drugs for anxiety disorder. [41] Due to the limitation of this review, the details of these treatments will not be described as they were already published in other articles.

4. Conclusion

Anxiety disorder is a disease that seriously affects life and health. Studies have shown that environmental changes, childhood trauma, food, and other factors are closely related to anxiety. Genome-wide studies have uncovered five new loci and variants in the PDE4B gene, which added to the understanding of anxiety. Numerous studies have shown that 274 genes interact with environmental exposure and influence social anxiety symptoms. Scientists found molecule such as the brain receptor GPR158, MicroRNA-137, and the interleukin-17a (IL-

17a) cytokines that showed evidence of increasing anxiety behaviors. Currently, the treatment of anxiety mainly focuses on psychotherapy, drug therapy, and animal-assisted therapy. As shown in the meta-analysis, cognitive behavioral therapy can improve the condition and reduce anxiety symptoms; the effect was more pronounced in PTSD, and the impact in GAD and SAD was small to moderate. Mindfulness-based cognitive therapy and internet behavioral therapy (iCBT) were both effective in reducing GAD and other anxiety symptoms. In terms of lessening the severity of SAD in kids and teenagers, iCBT was more feasible and affordable than ISUPPORT. Pharmacotherapy, on the other hand, like antidepressants, includes various types of SSRIs and SNRIs that are safe, effective, or well tolerated. Also, dog walking reduced state and trait anxiety, fear, and resting heart rate. Lastly, the CBD, the potential molecule therapeutics, and the fear extinction mechanisms and multiple innovated approaches are promising treatment for anxiety disorders. The findings may be helpful for people with anxiety disorders or parents looking for the proper medication for a child or teen with an anxiety disorder. A closer examination of pertinent information is required to increase the precision of the conclusions.

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