RECENT ADVANCES IN THE PHARMACOLOGICAL MANAGEMENT OF ANXIETY: FROM TRADITIONAL MEDICATIONS TO NOVEL THERAPEUTIC AGENTS

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Abstract

Anxiety disorders are the most prevalent psychiatric disorders and the primary cause of disability. The initial objective of this review is to provide a comprehensive overview of the current pharmacological treatments (both approved and off-label), including selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and GABAergic medications (benzodiazepines, pregabalin, and gabapentin), which are widely regarded as first-line pharmacological treatments for anxiety disorders. Investigate potential pharmacotherapeutic medications that are currently under development for the treatment of anxiety disorders in adult patients. The neurotransmitters and pathways that have been examined include psychedelic substances that follow the serotonergic pathway, modulators of the GABAergic system, neuro-steroids, therapies based on cannabinoids, and natural medications. The safety and tolerability of contemporary pharmacological treatments for anxiety disorders have progressed significantly compared to three decades ago. In summary, the progress in Traditional Pharmacological Treatments and new Pharmacotherapies research in anxiety disorders suggests the need for further investigation of these innovative approaches and larger-scale investigations of potential candidates with positive results from smaller trials.

Keywords: Anxiety Disorders; Benzodiazepine; Psychedelics; SNRIs; SSRIs

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Introduction

Anxiety disorder is a specified type of mental health issue, its widespread occurrence in humans and its manifestation in various anxiety disorders makes it a significant area of specialization in therapeutic practice. In recent years, our knowledge of anxiety disorders has been greatly enhanced by progressions in the fields of nosology, epidemiology, and psychobiology. Significant progress in the field of medication and psychotherapy for these diseases has provided patients with practical optimism for alleviating symptoms and enhancing their overall functioning. Anxiety disorders inflict significant distress on patients, impose a substantial strain on their families and society resources, and actively contribute to the emergence of depression, drug addiction, physical diseases, and other negative consequences (First, 2010). In Europe in 2010, the combined expenses of medical health care use, sick leave, early retirement, and decreased job productivity amounted to almost €75 billion highlighting the significant financial impact resulting from anxiety disorders. "European Study of the Epidemiology of Mental Disorders research" reveals that a mere 20 percent of individuals diagnosed with an anxiety disorder actively seek assistance from healthcare providers, and a small fraction of those individuals really get sufficient therapy.

Currently, the primary treatment modalities are psychotherapy, which has shown efficacy in anxiety disorders, and medication. Regarding individuals who undergo therapy, significant challenges persist in terms of non-compliance, non- or partial response, and recurrence. Neurostimulation techniques, including as electroconvulsive therapy, transcranial magnetic stimulation, vague nerve stimulation, and deep brain stimulation, may be explored for treatment-resistant individuals who exhibit little or no progress with pharmaco- and/or psychotherapy. Collectively, there is a pressing want for the refinement of innovative methodologies in the management of anxiety and associated disorders (Trivedi, 2004). The objective of this review is to examine the latest progress in the pharmacological treatment of anxiety, including both conventional drugs and innovative therapeutic agents.

The search criteria used in the preparation of the review article titled "Recent advances in the pharmacological management of anxiety: From traditional medications to novel therapeutic agents" are critical for ensuring the rigor and relevance of the included literature. Below are the essential components of the search methodology that should be included in the introduction section of the review.

A systematic search for relevant literature was performed across multiple reputable databases to gather comprehensive and current information on management of anxiety. The databases utilized in the literature search include:

PubMed, Google Scholar, Scopus, Web of Science. To ensure a broad retrieval of pertinent literature, the following keywords were employed in various combinations are Anxiety Disorders, Benzodiazepine, Psychedelics, SNRIs, SSRIs.

Anxiety Disorders

Anxiety, originating from the Latin word "anxieties" meaning to choke, throttle, bother, and disturb, refers to the complex range of behavioural, emotional, and cognitive reactions to the sense of

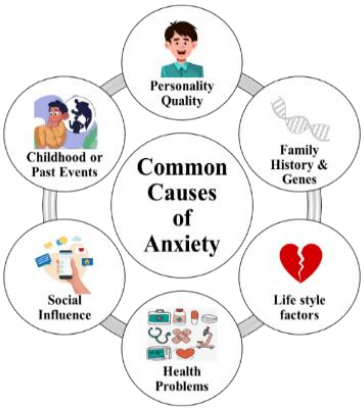

Figure 1. Common causes of Anxiety

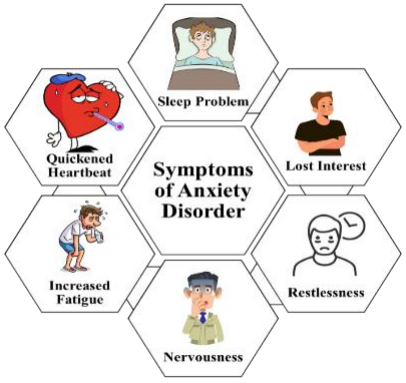

Figure 2. Symptoms of Anxiety Disorder

threat (Figure 1). Anxiety is a typical human psychological state. Anxiety, when experienced in moderation, triggers a vigilant and flexible reaction to difficult or stressful situations (Figure 2). Superfluous anxiety disrupts the equilibrium of the person, leading to a dysfunctional condition. Excessive or pathological anxiety is defined as manifesting in the absence of challenge or stress, when it is disproportionate to the challenge or stress in terms of duration or intensity, when it causes substantial distress, and when it leads to psychological, social, occupational, biological, and other impairments (Figure 3).

The "National Comorbidity Survey Replication" (NCS-R) rates anxiety disorders as the most prevalent category of mental diseases in the United States, with a lifetime prevalence of around 32% (Kessler *et al*., 2005). The two most prevalent anxiety disorders are social anxiety disorder and particular phobia. According to the World Health Organisation, the worldwide prevalence of anxiety disorders is estimated to be at 264 million individuals, indicating a 15% rise since 2005 (World Health Organization, 2017). Due to its higher incidence, anxiety may result in job and school absences and impose a greater financial burden than other mental diseases (Alonso *et al*., 2004; Ahola *et al*., 2011; Drost *et al*., 2013). Despite this, in the last five to ten years, there has been a mostly smaller amount of research on novel pharmacological treatments for anxiety disorders than there has been on treatments for major depressive disorder, bipolar disorder, and schizophrenia in experimental drug trials.

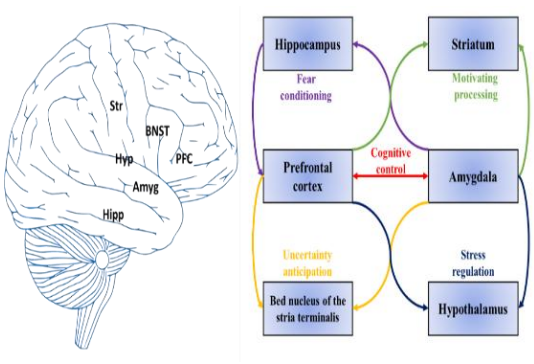

Figure 3. Anxiety-related functional systems and brain structures

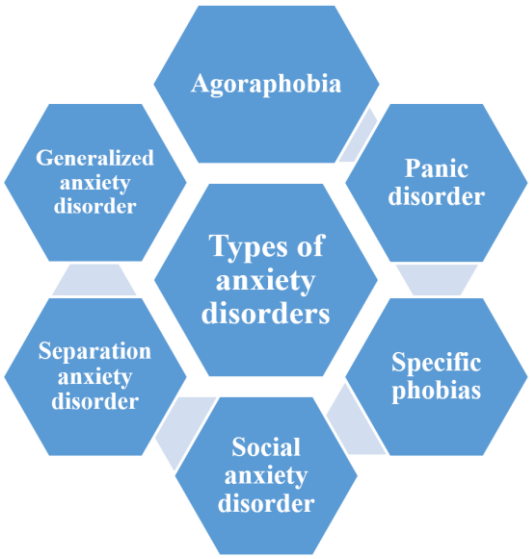

Figure 4. Categories of anxiety disorders

Types of Anxiety Disorders

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published by the American Psychiatric Association identify various categories of anxiety disorders (Figure 4).

Epidemiology

The prevalence of anxiety disorder in populations is subject to significant variation across large-scale studies as a result of methodological differences (Copeland *et al*., 2014; Ormel *et al*., 2015; Bandelow and Michaelis, 2015). However, these disorders are not necessarily severe or need medical treatment. Within a year, only 10%–14% of adults meet the DSM criteria for anxiety disorder. The most common phobia is specific phobia, which is followed by agoraphobia, panic disorder, and social anxiety disorder. Those between the ages of 18 and 25 had the greatest frequency of anxiety disorders after a year. There is no evidence of a rise in the prevalence of anxiety during the last 20 years in the few methodologically sound investigations of temporal trends (Wittchen *et al*., 2011). However, the maturing perceptions of the effects of anxiety disorders may be influenced by the growing awareness, pursuance of, and provision of treatment. Large-scale research has shown that high-income nations have the highest frequency of anxiety disorder. There were 27 nations where the World Mental Health Surveys were done (Ruscio *et al*., 2017; Stein *et al*., 2017; Wardenaar *et al*., 2017). However, all nations have consistent sociodemographic correlations. It is important to remember that women have anxiety disorders at a rate that is 1-3–2-4 times higher than that of men. This discrepancy becomes noticeable after puberty

and is especially noticeable throughout development. Anxiety disorders are also more prevalent among individuals who are unemployed, have low education, low income, or are unmarried (Silove *et al*. 2016; Roest *et al*. 2019).

According to epidemiological research, anxiety disorders have a relatively high one-year to lifetime prevalence ratio, indicating a chronic recurring character. The symptoms of anxiety disorders might last for years in some patients. Over 70% of those with a single anxiety disorder had a two-year remission from generalized anxiety disorder and panic disorder without agoraphobia (Hendriks *et al*., 2013). Anxiety disorders have a negative impact on mental health, but they may also be associated with unstable relationships, reduced functioning, and higher rates of absence from work when compared to those without these disorders. These factors have substantial economic repercussions and can influence somatic health (Meier *et al*., 2016; Momen *et al*., 2020). Increased comorbid anxiety in individuals with somatic diseases has been linked to poor treatment adherence, unhealthy lifestyles, and dysregulations of psychobiological stress systems. Therefore, the incorporation of somatic health considerations early in the treatment of anxiety disorders is essential.

Evolution of Pharmacological Treatments

Psychosurgery

The oldest evidence of suspected psychosurgery date to the Neolithic period, when trephination and healing marks were found on many skulls, suggesting that these early operations were probably carried out with therapeutic intentions. While some specimens have been discovered to contain contemporaneous fractures, many other skulls do not exhibit any signs of trauma (Stone and Miles, 1990). Early trephination may have been used for ceremonial or spiritual purposes, curing mental illnesses, epilepsy, and migraines (Robison *et al*. 2013).

Psychosurgery was frequently discussed in Renaissance medical literature and artwork, most notably in Hieronymus Bosch's painting "The cure of folly or the operation for the stone," which suggested that a physical stone within the brain caused mental sickness (Dimopoulos *et al*., 2008). Psychosurgery was almost eradicated from Western medicine for many centuries before making a comeback in the contemporary period. Growing curiosity was sparked by new findings concerning functional neuroanatomy and neurophysiology during the 1800s (Pichierri *et al*., 2012). The idea that brain activity and anatomy are related was expanded upon by ground breaking research on motor cortex localization, despite the fact that phrenology was flawed and finally abandoned. There after displayed aggressive and impulsive behaviour, is the most well-known illustration of the importance of studying patients with traumatic brain injuries (Simpson, 2007).

Stereotactic Neurosurgery

As the morbidity and death rates associated with lobotomies gained more public and professional recognition, public opinion began to shift against them. In addition to minimally invasive lesioning and resections, the medical community sought more rigorously scientific surgical procedures based on hypothesis-driven targeting. A neurosurgeon who used selective undercutting of the orbitofrontal cortex developments in stereotactic neurosurgery was among the first to embrace these notions; this led to even greater gains when open and closed lesioning techniques were replaced (Scoville, 1949). Using X-ray ventriculography, the thalamic dorsomedial nucleus was the target for treating psychosis and agitation. The limbic leucotomy, sub caudate tractomy, capsulotomy, and stereotactic cingulotomy are examples of later advancements in psychosurgical stereotaxis. It was discovered that in order to alleviate symptoms, targeted lesions of white matter networks and grey matter structures were less invasive and equally effective as eliminating the whole frontal lobe (Lapidus *et al*., 2013).

Cingulotomies include boring the cingulum bundle's white matter fibers after severing the cingulate gyrus. They are used to several illnesses. Since then, the cingulotomy has been used to treat chronic, persistent pain and depression that is resistant to therapy for obsessive-compulsive disorder (Scoville, 1949). Disruption of cortico-striate-thalamocortical circuitry is regarded to be one of the therapeutic advantages of cingulotomy, which is still the most common psychosurgical procedure performed in North America.

Because anterior capsulotomy disrupts front thalamic fibre connections, it has also been shown to be helpful in treating OCD. Gamma knife radiosurgery or radiofrequency coagulation may be used. The thalamic and limbic connections of the orbitofrontal cortex are impacted by sub-caudate tractotomy, which has its roots in Scoville's orbitofrontal corticectomy (Scoville, 1949).

Pharmacology's Growth and Psychosurgery's Fall

There are many reasons why psychosurgery did not gain as much traction in the 1950s. The early public excitement for frontal lobotomies stemmed from both Freeman's outstanding lobbying and marketing skills and the general acceptance of the procedure. This led to a lax approach to psychosurgery, with non-neurosurgeons treating patients under unsuitable circumstances. Professional criticism was levelled at this because of the significant adverse events that are often unreported and the lack of impartiality and scientific rigor (Hoffman, 1949). Additionally, it became clear that some sick or handicapped people had their lobotomies performed without their knowledge or permission, and those criminals could have been treated for dysfunctional conduct rather than mental illness.

Psychosurgery made a substantial contribution to the development of contemporary research ethical guidelines. But with the development of pharmacology and the introduction of lithium and chlorpromazine treatment, psychosurgery finally suffered a setback (López-Muñoz *et al*., 2005). Psychosurgery therefore lost popularity, but psychopharmacology flourished as strong sales led to more funding and research. Rapid development and licensing of more antipsychotic and antidepressant medications shown that pharmaceutical treatment outperformed psychosurgery in terms of effectiveness, safety, and cost.

Current Psychopharmaceutical Interventions

Medications and psychotherapy are the usual first therapies for mental illnesses. Pharmacological agents that are frequently implemented include (Gitlin, 2006). However, the widespread problem of therapy resistance or failure requires the use of other therapies. The first step is often to improve drug dose or timing, or to switch to a different therapeutic class (Rush *et al*., 2006). The same is true for a large proportion of people with cancer, OCD, or bipolar illness (Cheung *et al*., 2007). People who have poor response to therapy often experience more pronounced symptoms and face an elevated risk of disease and mortality.

Traditional Pharmacological Treatments

Benzodiazepines

Benzodiazepines have been used in therapeutic settings as sedatives and hypnotics (Table 1). Early benzodiazepines, such as diazepam and chlordiazepoxide, had a better safety profile than barbiturates (Wick, 2013). Benzodiazepines were originally marketed as having a reduced dependency risk than barbiturates. The diazepam becoming the most often prescribed medicine in the United States and Europe (Licata and Rowlett, 2008). A major clinical problem was discovered as benzodiazepine dependency. Newer 'benzodiazepine-like' medicines, such as zopiclone, and zolpidem were released in the 1980s with the purpose of lowering addiction risk. Nevertheless, these more modern drugs have been connected to dependency and misuse (Victorri-Vigneau *et al*., 2014).

Pharmacology and Clinical Effects

Efficacy and Dependence Liability

It has been shown that diazepam, flunitrazepam, and midazolam exhibit dose-dependent reinforcing effects in anxiety patients (Bai *et al*., 2011), as well as abuse potential in people (Carter *et al*., 2007). Certain traits are linked to higher levels of benzodiazepine self-administration in experimental settings. It has been shown that the way benzodiazepines affect healthy teenagers differs according to how much they want sensations. Individuals with greater sensation-seeking scores reported stronger sedative effects from diazepam, while those with lower scores reported lower ratings, indicating a risk of abuse (Kelly *et al*., 2009). Diazepam has also been shown to be more reinforcing for those who suffer from social anxiety and under anxiety-inducing experimental situations, as well as more reinforcing than buspirone in moderate alcohol users. Similarly, anxiety levels in anxiety patients were shown to be strongly linked with alprazolam self-administration levels under double-blind settings. In contrast,

Table 1. Shows Half-lives of benzodiazepines and dosage correspondence

Benzodiazepines with brands	Half-life	Dose comparable to 5 mg of diazepam
Flunitrazepam: Hypnodorm®, Rohypnol®	Intermediate	0.5
Temazepam: Euhypnos®, Normison®, Temaze®	Short	10
Alprazolam: Kalma®, Xanax®	Short–intermediate	0.5
Oxazepam: Alepam®, Murelax®, Serepax®	Short	15
Diazepam: Antenex®, Ducene®, Valium®	Long	5

at the doses tested, triazolam did not operate as a reinforcer among cannabis users. However, participants' estimates of their want to take the drug again and readiness to pay for it, which are often related with abuse liability, had a significant impact. That the probability of benzodiazepine use may be influenced by disparities in characteristics and substance use (Lile *et al*., 2010).

Benzodiazepines have a lower addiction potential than other drug categories, including opioids, barbiturates, cocaine, and GHB, despite their capacity to maintain self-administration. Additionally, substances that have a rapid onset of action and shorter half-lives may have more potent reinforcing effects. The probability of misuse is increased by neuroadaptation and physical dependence, which are consequences of prolonged use. Misuse and dependency are regularly documented among patient groups, either alone or in combination with other medicines, despite their reduced proclivity for self-administration compared to other drugs. Although not all individuals acquire benzodiazepine dependency after long-term usage, it may occur in as little as a week (Woods *et al*., 1991).

SSRIs (Selective Serotonin Reuptake Inhibitors)

MOA of the SSRIs

As inhibiting presynaptic selective enzyme release technology increases serotonin levels in the synaptic cleft, which contributes to the therapeutic benefits of selective serotonin reuptake inhibitors and other antidepressants. Selective serotonin reuptake inhibitors significantly enhanced depression treatment. Because selective serotonin reuptake inhibitors have far higher selective enzyme release technology specificity than MAOIs and TCAs (Xue *et al*., 2015). When it comes to suppressing selective enzyme release technology, escitalopram is nearly twice as effective as its counterpart, citalopram, and has the highest specificity of any selective serotonin reuptake inhibitors. The half-lives of the selective serotonin reuptake inhibitors in steady state depend on whatever particular drug is used (Rao, 2007). For example, fluoxetine has a half-life of one to four days. The half-life of paroxetine is around 21 hours, while that of citalopram is approximately 26 hours. The pharmacokinetics of sertraline and citalopram are linear, whereas those of fluoxetine, fluvoxamine, and paroxetine are nonlinear (DeVane, 1998).

The liver's cytochrome P450 system is in charge of breaking down SSRIs. Sertraline, fluoxetine, and fluvoxamine all strongly block certain cytochrome P450 enzymes, which may lead to more drug-drug interactions than citalopram and escitalopram. That nonlinear kinetics at higher dosages may be caused by the suppression of one's own metabolism by fluoxetine, paroxetine, and maybe fluvoxamine (Catterson and Preskorn, 1996). The molecule has a half-life of four to six days, whereas norfluoxetine, its active metabolite, has a half-life of seven to fifteen days (Rossi *et al*., 2004). Fluoxetine has the longest half-life of all the selective serotonin reuptake inhibitors. For a patient with inadequate medication elimination, sertraline and citalopram could be preferable options because of their linear kinetics upon starting therapy. Paroxetine and fluoxetine are the two SSRIs that inhibit CYP2D6 the greatest; the other SSRIs do not inhibit this enzyme. There don't seem to be any notable interactions between SSRIs and CYP3A4.

Clinical Outcomes and Side Effects of SSRIs

The selective nature of the SSRIs and their lack of interaction with other receptors, including histaminic, cholinergic, dopaminergic, and noradrenergic, are the reasons for their enhanced tolerability. At the sub-receptor level, serotonin receptors are further divided into at least seven classes. These receptors regulate a diverse array of functions that are not associated with mood, such as sleep, appetite, and sexual function, as well as symptoms such as anxiety, depression, pain, and vertigo (Nelson, 1997). An increase in the inhibition of serotonin reuptake makes more of the neurotransmitter accessible for interaction with any of these receptors or subtype receptors. Serotonergic actions are therefore the primary culprit behind the bulk of SSRI side effects, which vary with dosage (Goldstein and Goodnick, 1998).

Adverse Effects of SSRIs

Selective serotonin reuptake inhibitors are generally more well-tolerated than other antidepressants, they may cause agitation, nausea, regurgitation, insomnia, lethargy, headache, and decreased sexual drive (Chu and Wadhwa, 2020). Extrapyramidal symptoms serotonin syndrome, QT prolongation, dermatitis, birth defects, hyponatremia, and cataracts are among the less frequent adverse effects of selective serotonin reuptake inhibitors.

SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)

Mechanism of Action of SNRIs

Serotonin and norepinephrine reuptake inhibitors have a dual mode of action, selectively inhibiting the reuptake of 5-HT and norepinephrine from the synaptic clefts by binding to 5-HT and norepinephrine transporters. As thus, they increase these neurotransmitters' availability in the central nervous system. The possibility of treating central serotonergic and noradrenergic dysfunctions, which are thought to play a major role in the etiology of anxiety disorders, justifies the use of Serotonin and norepinephrine reuptake inhibitors. Moreover, Serotonin and norepinephrine reuptake inhibitors gain from their capacity to concurrently influence a number of functional features that some authors link to certain monoamines, such as aggressiveness to 5-HT and motivational deficiencies to norepinephrine (Mowla *et al*., 2016). The following agents are currently included in the class of Serotonin and norepinephrine reuptake inhibitors: duloxetine, milnacipran, and desvenlafaxine, the active metabolite of venlafaxine (Table 2).

Emerging Pharmacotherapies

Psychedelic Compounds

Psychedelics are a kind of drug that cannot be fully understood without drawing on a range of disciplines, including anthropology, ethnopharmacology, psychiatry, psychology, sociology, and others. Psychedelics may be the oldest kind of psychopharmacological agent known to man. Soma, a substance used in ancient India, was highly regarded and widely mentioned in the Rigveda, with multiple Vedic chants produced in its favour.

There is rising interest in using psychedelic substances to treat anxiety problems, such as depression, drug use disorders, and some forms of headaches (Nutt and Carhart-Harris, 2021). The medications used today to treat neuropsychiatric disorders require days or weeks to start working and need to be taken consistently over time to provide long-term effects. On the other hand, the potential benefit of psychedelic therapy is that a single or two doses of a psychedelic may provide immediate and lasting effects. The psychedelic renaissance is the selection of a drug from the wide range available. The most well researched psychedelic substances so that you may make educated decisions. SPs cause substantial shifts in consciousness, including a variety of perceptual changes (Nichols, 2018).

Serotonergic Pathways (SPs) and Anxiety Relief

Their unique psychoactive properties may be due, in part, to the different manner in which mescaline bind to various receptors, including 5-hydroxytryptamine, dopamine, sigma, and trace amine-associated receptors. The 5-hydroxytryptamine receptors are highly receptive to SPs (Rickli *et al*., 2016). While mescaline acts on 5-hydroxytryptamine 2 receptors, LSD attacks dopamine receptors directly as well. It is unclear how S and TAAR receptors, which DMT binds to, contribute to the behavioural effects of DMT (Ray, 2010). While the exact role of individual 5-hydroxytryptamine receptors in SP activity is still unclear, it is thought that affinity for 5-hydroxytryptamine 2C and 5-hydroxytryptamine 2B might contribute to potential side effects including weight gain or cardiac problems that could arise with long-term use (Neumann *et al*., 2023). There is mounting evidence that the 5-HT2A

Table 2. Shows pharmacokinetics of SNRIs

Drugs	Therapeutic dose range (mg/day)	Bioavailability	Biotransformation pathways	Major metabolites	Half-life	Elimination routes	Protein binding
Venlafaxine IR/SR	75–225 (divided dose IR) (single dose SR)	45%	CYP2D6 and others	O-desmethyl-venlafaxine	4 h	Urine (87%)	27% (parent)
Desvenlafaxine (ODV)	50	80.5%	CYP3A4	No active metabolites	10 h	Urine unchanged,	30%
Duloxetine	60–120	50%	CYP2D6 and CYP1A2	4-hydroxy duloxetine glucuronide	12 h	Urine unchanged	>90% (parent)
Milnacipran	25–200	85%	CYP2D6 or CYP2C19	No active metabolites	12 h	Urine unchanged (50%)	13% (parent)

receptor agonist properties of SPs are crucial in mediating the psychedelic effects of these medications (Glennon *et al*., 1986). To start, 5-hydroxytryptamine 2AR affinity is significantly associated with SP potency in vivo. Furthermore, when administered psychedelics to 5-hydroxytryptamine 2AR mutant mice, the head-twitch response-a behavioural proxy for 5-hydroxytryptamine 2AR activity hypothesized to coincide with psychedelic effects-is absent (Glennon *et al*., 1986). Thirdly, the psychedelic effects of psilocybin and LSD are mitigated by the 5-HT2A/CR antagonist ketanserin. Psychedelic effects of SPs may be due to mechanisms downstream of 5-hydroxytryptamine 2AR activation, as 5-hydroxytryptamine 2AR agonists like lisuride and ergotamines do not produce such effects (Adams and Geyer, 1985).

The difference between 5-hydroxytryptamine 2AR agonists that are psychedelic and those that are not have been linked to biased agonism, or the selective activation of downstream pathways. The biase dagonism of SPs may be explained by a number of 5-hydroxytryptamine 2AR-related processes (Berg *et al*., 1998).

GABAergic Modulators

GABAergic modulators are compounds that affect the action of the neurotransmitter gamma-aminobutyric acid in the brain. Gamma-aminobutyric acid is the central nervous system's major inhibitory neurotransmitter, which means it decreases neuronal excitability and helps to calm it. GABAergic modulators function by boosting or decreasing Gamma-aminobutyric acid activity at its receptors, which may result in a variety of effects such as anxiety reduction, sedation, sleep promotion, and seizure control. Gamma-aminobutyric acid receptor modulators may be endogenous or exogenous. Endogenous modulation of neuronal excitability shows that endogenous ligands and/or anomalies in Gamma-aminobutyric acid-benzodiazepine receptor use in the pathophysiology of anxiety disorders.

Endogenous Modulators

Benzodiazepines and Neuro-steroids

Although benzodiazepines are found in many species, including humans, they are not well understood in relation to treating anxiety disorders. Rather, think about how well exogenous benzodiazepines work. GABA receptors and some G-protein-coupled receptors are neuromodulated by neuro-steroids, which are generated from progesterone. Similar to benzodiazepines, the neuro-steroids allopregnanolone and pregnanolone have an inhibitory and anxiolytic effect. Tetrahydro progesterone could have the opposite effect. It has been shown that mice under experimental stress exhibit changed brain and plasma neuro-steroid concentrations as well as downregulated GABA receptors. Pre-treatment with anxiolytics attenuated the effects of stress (Biggio *et al*., 1990).

Exogenous Modulators: Benzodiazepines:

GABA system abnormalities are linked to panic disorder, which may be effectively treated with benzodiazepines. Benzodiazepines as a group have a variety of pharmacologic effects on the GABA receptor. They may act as a full inverse agonist, a partial inverse agonist, an antagonist, or a partial agonist. conflicting results when using benzodiazepines with different pharmacologist to learn more about the role of GABA in anxiety disorders.

Novel GABAergic Agents

GABAergic neurotransmission may also be increased by boosting GABA production and release (e.g., gabapentin) while blocking GABA reuptake (e.g., tiagabine).

Increase GABA Release: Gabapentin:

Early research on the effectiveness of gabapentin in treating anxiety disorders is positive. By boosting the release of non-synaptic GABA from glia, gabapentin raises GABA activity. While gabapentin does not seem to act on GABA receptors, it has structural similarities with GABA. Many mental illnesses have shown potential for treatment with gabapentin, such as pain syndromes, bipolar disorder, intermittent explosive disorder, and anxiety disorders including PTSD, panic disorder, social anxiety, and generalized anxiety disorder (Pollack *et al*., 1998; Ketter *et al*., 1999). The observed negative effects aligned with the recognized gabapentin side effect profile.

Inhibition of GABA Reuptake: Tiagabine:

Tiagabine, the only selective GABA-reuptake inhibitor (SGRI) available today, raises GABA levels by inhibiting GABA reuptake. Clinical trials of tiagabine in individuals with refractory anxiety have revealed that it may be useful in treating anxiety disorders, particularly panic disorder (Bremner *et al*., 1995).

Neuro-steroids

A cholesterol emulsion injected into cats produced drowsiness, marking the first isolated discovery of a distinct action of steroids on excitable cells. This finding was noteworthy because of the chemical properties of cholesterol and other lipids, which need organic solvents for solubilization. The same effect was studied in a controlled, experimental setting and expanded upon a year later (Selye, 1942). When it comes to the way neurons work, progesterone acts like an anaesthetic. Even though these studies showed a lot of promise, researchers spent the next 30-40 years figuring out what was going on physiologically and how to apply these effects to humans. The steroids were thought to have their action by perturbing lipid membranes, hence affecting neuronal activity (Lawrence and Gill, 1975). The intricacy and variability of biological membranes made this hypothesis difficult to establish or reject. Despite abundant understanding now about the direct activity of steroids at specific places and receptors on the plasma membranes of cells, this notion cannot be completely discarded.

Cannabinoid-Based Treatments

Cannabis usage is often related with stress alleviation and mood enhancement. However, in rare circumstances, it causes dysphoric consequences such as panic or heightened anxiety. The bidirectional effects of cannabis found in humans may be replicated in experimental animals, with low doses anxiolytic and high levels anxiogenic (Viveros *et al*., 2005). Oral delivery of Δ9-THC is unlikely to cause unpleasant symptoms like anxiety and panic, which are common with cannabis smoking. Oral Δ9-THC has been shown to diminish amygdala reactivity in healthy volunteers exposed to social cues of danger, comparable to anxiolytic medications like benzodiazepines (Dejean *et al*., 2015). However, contradicting findings have also been reported. Large and well-designed controlled studies, however, are required to properly define the potential role of cannabis as an adjuvant or alternative therapy to traditional methods to PTSD care.

Multimodal Antidepressants

Multimodal antidepressants are more efficacious than previous medications that typically focus on a single neurotransmitter system (such as serotonin or norepinephrine) by targeting many pathways or biological processes in the brain to relieve anxiety and depression. Relevant multimodal antidepressants for the treatment of anxiety disorders includes the followings.

Vilazodone

Vilazodone is a new class of chemicals showing potential in treating anxiety via a dual-action mechanism. Vilazodone has a notable preferential binding to 5-hydroxytryptamine 1A receptors and demonstrates a substantial and specific inhibition of serotonin 5-hydroxytryptamine reuptake (Wang *et al*., 2013). The binding affinity of vilazodone to the 5-hydroxytryptamine reuptake site is much greater than that of dopamine or norepinephrine reabsorption sites (Stahl, 2005). Accordingly, vilazodone acts as a partial agonist of 5-HT 1A and a specific inhibitor of serotonin reuptake. An exclusive group of antidepressants with a distinct mode of action is now being recognized as serotonin partial agonist reuptake inhibitors (Dawson and Watson, 2009). Vilazodone works similarly to selective serotonin reuptake inhibitors in that it selectively inhibits serotonin's reuptake, which raises serotonin levels in the synaptic tissue and relieves symptoms of anxiety disorder. Additionally, endogenous serotonin's adverse effect is reduced by the partial agonist activity of the 5-hydroxytryptamine 1A receptor, which may enhance vilazodone's antidepressant effects.

Although serotonergic neurotransmission is somewhat inhibited by the 5-hydroxytryptamine 1A receptor, it is unknown how this affects the therapeutic activity of antidepressants. Research, however, suggests that the effects of postsynaptic and presynaptic 5-hydroxytryptamine 1A receptors on 5-hydroxytryptamine release are different. Auto-receptors located on raphe nuclei are known as presynaptic receptors. The ring and secretion of 5-hydroxytryptamine are decreased during activation of these receptors. Extended 5-hydroxytryptamine stimulation of 5-hydroxytryptamine 1A receptors may cause functional loss of sensitivity in auto-receptors, but not in postsynaptic receptors. Therefore, an increase in serotonin levels across the board may cause the 5-hydroxytryptamine 1A auto-receptors to become desensitized and the 5-hydroxytryptamine 1A postsynaptic receptors to become activated, which would then co-exacerbate the symptoms of anxiety disorder. The delayed response to antidepressant medication, such as SSRIs, is thought to be mostly caused by 5-hydroxytryptamine 1A auto-receptors inhibiting serotonin release. This is because, with long-term SSRI medication, it takes time to overcome

the suppression of serotonin and the downregulation of 5-hydroxytryptamine 1A auto-receptors. Vilazodone has the potential to provide a more thorough and quick desensitization of 5-hydroxytryptamine 1A auto-receptors without too activating the 5-hydroxytryptamine 1A auto-receptor-mediated inhibition of serotonin release via its partial agonist action at 5-hydroxytryptamine 1A receptors (both presynaptic and postsynaptic) (Hughes *et al*., 2007). In the end, this lessens the 5-hydroxytryptamine neurons' negative feedback loop via the auto-receptor. Increased serotonin release from stimulating postsynaptic 5-hydroxytryptamine 1A receptors might enhance the SSRI effects of serotonin.

Vortioxetine

Vortioxetine (Trintellix) is a new addition to the SSRI family that expands its receptor activity. There is continuous disagreement regarding which category to place this unusual SSRI in. Traditionally, serotonin antagonist reuptake inhibitors (such as trazadone and nefazodone) show some action in norepinephrine reuptake inhibition; however, this medication does not. It may enhance acetylcholine and histamine levels by partially antagonizing 5HT1B; glutamate levels by antagonizing 5HT3; and acetylcholine and norepinephrine levels by antagonizing 5HT7 (Cuomo *et al*., 2024). All of these effects have the potential to provide favorable cognitive consequences, which would be very beneficial for many individuals suffering from chronic pain. At the same time, glutamatergic activity may contradict therapeutic aims for the patient, since pain practitioners often want to minimize NMDA activity.

Clinical Efficacy and Safety

Multimodal antidepressants, such as vortioxetine and vilazodone, have been demonstrated to be equally effective as SSRIs and SNRIs in treating depression and anxiety disorders. They provide additional advantages, notably in terms of reducing cognitive symptoms such as memory and concentration problems, which are often linked with depression. Vortioxetine, in example, has been shown to be beneficial in treating both mood and cognitive symptoms of depression, but vilazodone may have a speedier beginning of action. These medications are helpful in lowering depression and anxiety symptoms, and provide a more comprehensive approach to therapy than standard antidepressants (Sanchez *et al*., 2015).

Multimodal antidepressants, such as vortioxetine and vilazodone, are typically well accepted and have a better safety profile than previous antidepressants like SSRIs and SNRIs. They are connected with less sexual side effects, less weight gain, and lower levels of drowsiness. Common adverse effects include nausea, dizziness, and sleeplessness, which are usually minor and temporary (Deardorff and Grossberg, 2014). Serious adverse effects are uncommon, however, like other antidepressants, they may raise suicide thoughts in younger people during the early stages of therapy. Overall, their safety profile makes them ideal for long-term usage, with less worries about side effects common to other antidepressants.

Anxiolytic Agents Beyond Benzodiazepines

Tricyclic Antidepressants (TCAs)

TCAs have been beneficial in treating anxiety disorders: amitriptyline works well for Post-traumatic stress disorder, imipramine for Parkinson's disease, clomipramine for Parkinson's disease and Obsessive-compulsive disorder. The limited safety and less desirable side effect profiles of TCAs in comparison to newer antidepressants limit their use in clinical practice. Through the inhibition of neurotransmitter reuptake, their therapeutic effects are hypothesized to be associated with elevated levels of synaptic serotonin and noradrenaline (Sinclair *et al*., 2009). This antidepressant family's multipotent blocking properties are one of the adverse effects that might make compliance more difficult. These include alpha-1 blocking effects, antihistamine effects and anticholinergic effects. These side effects, which include a brief increase in anxiety, usually go away in a few weeks (Lepola *et al*., 2003).

Buspirone

A partial agonist of the 5-HT1A receptor, buspirone is the first drug shown to be effective in generalized anxiety disorder. The first impact of this treatment is gradual, requiring many weeks for the therapeutic benefits to become apparent. Should a patient have recently used a benzodiazepine, their response is likely to be less positive. Generally safe and well tolerated, buspirone might induce early nausea, dizziness, restlessness, and tiredness (Chessick *et al*., 2006).

Mirtazapine

Mirtazapine enhances the levels of serotonin and noradrenaline in the synaptic terminals by suppressing auto-inhibitory alpha-2 receptors and specifically blocking postsynaptic 5-HT2 and 5-HT3 receptors. Contrary to SSRIs and SNRIs, it does not worsen anxiety symptoms and has the potential to enhance sleep by inhibiting histamine receptors (Szabo, 2001). Additional negative effects of antihistamines include stimulation of appetite and weight gain.

Beta Blockers

The significance of beta blockers in anxiety disorders is minimal, since they lack either basic or central anxiolytic characteristics. In some cases, such as in concert performers, they are used to manage the physical signs of performance anxiety, such perspiration, palpitations, and trembling, when these peripheral sympathetic effects are incapacitating (Papp, 2007). They have been utilized in the past, but RCT data is few. The fact that they have strong adverse effects, cannot be used by asthmatics, and may be overdosed makes them seldom recommended (Julien, 2013). In the case of performance anxiety, tremors are useful when they are present. drugs that fight depression Despite their history as strong tranquilizers, their significant side-effect profile and lackluster research support their current limited efficacy in treating refractory anxiety disorders. The results of using novel atypical drugs like olanzapine, risperidone, and quetiapine in individuals with treatment-resistant OCD and GAD have been inconsistent.4-D-cycloserine. Rats have shown improved fear-overcoming when administered this indirect NMDA glutamate receptor agonist. Height may accelerate behavior therapy's effectiveness, according to recent research on individuals with social anxiety.

Efficacy, and Limitations

Anxiolytic drugs, such as benzodiazepines, SSRIs, SNRIs, buspirone, beta-blockers, and gabapentinoids, are useful in treating anxiety but have significant limits. Benzodiazepines give quick relief, but they also entail the hazards of dependency, tolerance, and withdrawal, which restrict their long-term usage (Garakani *et al*., 2020). SSRIs and SNRIs are the first-line therapy for persistent anxiety, but they take weeks to work and may induce adverse effects such as sexual dysfunction and nausea. Buspirone has a decreased risk of dependency, but it takes longer to work and is less effective for severe anxiety. Beta-blockers alleviate physical anxiety symptoms but not emotional ones, whilst gabapentinoids and atypical antipsychotics are taken off-label or as adjuncts in treatment-resistant instances, raising concerns about side effects such as dizziness or metabolic difficulties. Most anxiolytics work better as part of a larger treatment strategy that includes therapy.

Comparative Overview of Treatments

Anxiety disorders manifest at an early age, even during childhood. Patients' interpersonal relationships and functionality are profoundly impacted by their enduring waxing and diminishing course throughout their lifetimes (Bandelow and Michaelis, 2015). Patients seek treatment in outpatient settings, either in medical or specialized mental health-care contexts, as the majority of pathological anxiety is underrecognized. The medical professionals pay more attention to serious mental diseases including psychotic disorders and drug use disorders that need hospitalization than they do to anxiety disorders. Not only that, but media coverage of depression and suicide attempts much outweighs that of anxiety, which ultimately leads fewer people to seek help for their worry. To manage or reduce anxiety symptoms, most doctors prescribe medication or psychotherapy. Psychological therapy and psychotropic medication should be administered together to individuals with very severe and disabling anxiety disorders (Craske *et al*., 2017).

Traditionally, various therapies have been prescribed for the treatment of varying degrees of anxiety and are classified as psychological treatment techniques. Psychotherapy include cognitive-behavioral, interpersonal, supportive, group, psychoanalytic, and short approaches. Evidence of cognitive-behavioral therapy's efficacy for a range of anxiety disorders. However, the benefit of new therapeutic modalities should be evaluated. Furthermore, the current population of mental health personnel is inadequate to accommodate the number of patients in need of treatment. Therefore, the community should be provided with a psychotherapeutic treatment for anxiety that is more cost-effective and accessible.

For the treatment of anxiety disorders, the benzodiazepine drug class, which includes chlordiazepoxide, has been the principal pharmacological agent for over sixty years. The introduction of these anxiolytic drugs was warmly received by both medical workers and worried patients. Because of the risk of side

effects, withdrawal syndrome, and reliance on benzodiazepines, patients in need of therapy have sought out less harmful therapeutic alternatives, which may not always work. Medications such as antidepressants, buspirone, beta-blockers, and antipsychotics are recognized as psychopharmacological agents. Thorough reviews and well planned clinical studies have shown their effectiveness (Gale and Oakley-Browne, 2000). It is usual practice to suggest a mix of psychological therapy and psychotropic medication for instances of extreme anxiety that cause impairment. Alternative medicine encompasses a wide range of practices, including aromatherapy, acupuncture, homoeopathy, massage therapy, yoga, focus, relaxation, and exercise (Wang *et al*., 2017; Alonso *et al*., 2018). Depending on the therapist's instructions, an active medicine, and physical manipulation are some of the modalities that a patient may undergo.

Clinical Trials

Clinical trials for drugs like benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), GABAergic modulators, and neurosteroids have significantly contributed to our understanding of their efficacy and safety in imaging anxiety and related disorders. Benzodiazepines, widely studies for acute anxiety management, demonstrate rapid symptom relief but are associated with dependency risks in long term use (Table 3). SSRIs and SNRIs have been extensively evaluated for generalized anxiety disorders (GAD), panic disorders, and social anxiety disorders, showing consistency efficacy in symptoms reduction and improved tolerability compared to older antidepressants.

Combining Psychotherapy and Medication

That compared to control groups, treatment groups that received either medicine or psychotherapy fared better. Comparing psychotherapy for anxiety disorders to a "wait-list," a control approach used in 70-75 percent of research including adults and children, provides the majority of the evidence in favor of the treatment (Bandelow *et al*., 2015; James *et al*., 2015; Patterson *et al*., 2016). In psychotherapy and pharmaceutical studies, the effect sizes of active and control conditions cannot be compared since pill placebos have bigger impact sizes than waiting controls. It was also shown that the pre-post effect sizes on average of capsule placebos were similar to the benefits obtained from psychotherapies. The effects, heterogeneity, or publication bias cannot explain this surprising outcome. However, because the average effect size attained with psychotherapies is still substantial, this does not imply that psychotherapy is unsuccessful. Instead, it implies that a placebo medication is a very successful course of therapy, at least in the first few weeks or months. However, it is imperative that patients are informed about the efficacy of the therapeutic alternatives that are at their disposal. However, there were only a few combination trials available for this comparison, and some of them did not use the most potent medications.

Table 3. Shows clinical trials and thier outcomes

S.no.	Drug Class	Clinical Trial Focus	Outcomes	references
1	Benzodiazepines	Evaluate for acute anxiety, panic attacks, and short-term relief in generalized anxiety disorders(GAD)	Rapid relief, effective in short-term use, but associated with dependency, tolerance and withdrawl symptoms.	Baldwin *et al*. (2013**)**
2	SSRIs	Assesed for long term management of GAD, panic disorder, social anxiety disorder, and obsessive-compulsive disorder (OCD)	Efeective in reducing anxiety symptoms with fewer side effects comparedbto older antidepressants ; delayed onset of action.	Bandelow *et al*. (2007)
3	SNRIs	Investigated for generalized anxiety disorder and comorbid depressive symptoms	Reduction; efective for both anxiety and depression, but may cause side effects like nausea and insomnia.	Fagan *et al*. (2023)
4	GABAergic Modulators	Targeting GABA-A receptors to enhance inhibitory neurotransmission.	Promising results in reducing hyperactivity in anxiety-related pathways; fewer dependency issues compared to benzodiazepines.	Rudolph and Knoflach (2011)
5	Neurosteroids	Evaluated as novel agents for anxiety and depression, particularly in postpartum depression.	Positive results in modulating GABA-A receptors, showing potential for rapid symptom releif with minimal side effects	Meltzer-Brody *et al*. (2018**)**

Challenges in Managing Anxiety Disorders

"Anxiety disorders" may be complicated by the presence of a variety of clinical symptoms, making identification and diagnosis difficult (DeVane *et al*., 2005). The majority of people with anxiety disorders do not get therapy for their difficulties. A community study conducted in a large Canadian city revealed that 30% of individuals with major depressive disorder sought treatment, while only 11 percent of those with anxiety disorder did likewise (Ohayon *et al*., 2000). However, only 32% perceived a necessity for professional treatment, and only 19% pursued it within a 12-month timeframe. The likelihood of patients seeking treatment was nearly three times lower for those with anxiety disorders alone than for those with both anxiety and mood disorders (Davidson *et al*., 1993).

Under-treatment:

Anxiety disorders are diagnosed, therapy may be suboptimal comprehensive, large-scale study conducted on psychiatric disorders in primary care (Sartorius *et al*., 1996). The most prevalent mental condition was a depressive disorder or an anxiety disorder with 4.6% of individuals suffering from both. Additionally, a quarter of the participants had an identifiable mental condition. Primary care physicians identified only half of the mental disorders, and only half of those disorders were treated. Additionally, inadequate psychotherapy services and inadequate medication compliance may arise (Wang *et al*., 2000).

Comorbidity:

Comorbidity is a particularly challenging aspect of anxiety disorder management, as individuals frequently have multiple anxiety disorders with overlapping symptoms (Davis *et al*., 2010). Moreover, there is often a connection between anxiety disorders and other mental health conditions like MDD. The elderly are more likely to have depression and anxiety (Flint, 2005), and comorbid problems are present in more than half of patients who see their primary care physician for mental health issues. People who had a dual diagnosis of anxiety and depression exhibited a significantly worse quality of life, psychosocial functioning, and occupational performance, as well as a higher degree of disease (Kessler *et al*., 1999). Chronicity was also significantly greater. Excessive medical consumption in primary care is also significantly correlated with comorbidity. Additionally, the prolonged duration of episodes and the elevated probability of recurrence that are attributable to comorbidities frequently necessitate long-term therapy (Hirschfeld, 2001).

Clinical Guidelines: Limitations and Benefits

Anxiety disorders have been successfully treated using both pharmaceutical and psychosocial approaches. Clinical guidelines may be especially effective in synthesizing existing evidence and offering clear recommendations to help clinicians and patients choose the best course of treatment (Baldwin *et al*., 2005). Guidelines may also incorporate diagnostic methods to aid in the investigation and identification of the kind of anxiety disorder and any associated conditions by practitioners. Because of these factors, recommendations and implementation techniques are being pushed more and more to enhance the treatment of depression and anxiety, particularly in primary care. Unfortunately, it is uncertain whether clinical recommendations have a major influence on clinical practice despite the time, money, and effort spent formulating and distributing them (Gilbody *et al*., 2003). To assist doctors in getting patients ready for and involved in treatment, as well as to help patients grasp the value of therapy and treatment adherence, additional tactics beyond recommendations.

Future Directions in Pharmacological Targets

While most of drug research focuses on increasing the effectiveness and tolerability of current anxiety drugs, significant resources have been committed in identifying new molecular targets during the last decade (Löw *et al*., 2000).

Refinement of Existing Pharmacological Targets

Postsynaptic 5-hydroxytryptamine 1A receptors cause anxious behaviours that are resistant to SSRIs. But as was already established, azapirones-whether total or partial 5-HT1A agonists-haven't shown to be any more efficacious than SSRIs over time. Similarly, it has been discovered that GABA-A subunits contribute to the anxiolytic effects of benzodiazepines (Ravindran and Stein, 2009). But after ten years of study, none of the agents that were being developed had made it to market; two had their development stopped because of

severe adverse effects. Eszopiclone, which is used as a hypnotic, works on GABA-A receptors to decrease anxiety as well 2, 3. When paired with an SSRI, eszopiclone had more specific anxiolytic effects than placebo in double-blind tests for PTSD and GAD. This effect is particularly intriguing in PTSD, when standard benzodiazepines are ineffective and perhaps hazardous (Belzung *et al*., 2001).

Novel pharmacological Targets

In addition to conventional drugs that target monoamine or Gamma-aminobutyric acid neurotransmitter systems, researchers are looking at whole new therapeutic techniques and biological targets, such as modulatory agents like neuropeptides (Madaan and Wilson, 2009). Their action is more specifically focused than that of antidepressants, implying a lesser risk of side effects (Roesler and Schröder, 2011). However, because of the difficulties in crossing the blood-brain barrier, not many neuropeptides have been successfully translated from animal models to human anxiety disorders. For the corporation, developing pharmaceutical medicines is a high-risk venture with historically poor returns that calls for a sizable time and financial commitment.

Conclusions

Anxiety disorders are widespread, persistent conditions that are often not fully acknowledged, incorrectly diagnosed, or with less than suitable treatment. Recent advances in the pharmacological treatment of anxiety show an important class drugs like benzodiazepines and SSRIs and toward innovative therapeutic agents. Emerging medicines like as glutamate modulators, neuro-steroids, and cannabinoid-based medications provide intriguing options that may have fewer negative effects. These developments are motivated by a better understanding of the neurological underpinnings that underpin anxiety disorders. While standard pharmaceuticals continue to be beneficial, the emergence of these innovative compounds offers promise for more tailored and focused treatments, catering to individuals who may not react well to conventional therapy. Further study is required to fully understand the promise of these novel therapy approaches. The review offers a comprehensive assessment of anxiety disorders, investigating both conventional and novel pharmaceutical therapies, as well as a thorough analysis of their mechanisms of action, effectiveness, and adverse effects. Recent discoveries elucidate the involvement of psychedelic drugs, serotonergic pathways, neurosteroids, and cannabinoid-based therapies in the management of anxiety, underscoring their promise in treating refractory patients. Furthermore, it underscores the efficacy of multimodal techniques and the integration of psychotherapy with pharmacotherapy as viable strategies to improve therapeutic results. This review's limitations, in comparison to previous research, stem from its dependence on existing clinical trial data, which may inadequately reflect long-term effects or the real-world application of newer therapies. Moreover, the discourse on the issues of managing anxiety and future directions, although thorough, would benefit from greater focus on the integration of tailored treatment frameworks.

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