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Review Article

Pharmacological breakthroughs in anxiety management: exploring traditional and emerging therapies

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ABSTRACT

Anxiety disorders are the most common psychiatric disorders and a significant cause of disability. While there is ongoing research into posttraumatic stress disorder (PTSD), depression and schizophrenia, there is a relative lack of innovative drugs being investigated for anxiety disorders. The first goal of this review is to summarize current pharmacological treatments (both approved and off-label) for panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD) and specific phobias (SP), which include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), antipsychotics, alpha- and beta-adrenergic medications (e.g., propranolol, clonidine) and GABAergic medications (benzodiazepines). Second, we will look at new pharmacotherapeutic drugs being investigated for the treatment of anxiety disorders in adults. The pathways and neurotransmitters reviewed include serotonergic agents, glutamate modulators, GABAergic medications, neuropeptides, neurosteroids, alpha- and beta-adrenergic agents and natural remedies.

Keywords: Anxiety disorders, Generalized anxiety disorder, Panic disorder, Social anxiety disorder, Specific phobias

INTRODUCTION

Mental health professionals recognize anxiety disorders as the most common form of mental illness. These conditions encompass a range of issues, including separation anxiety and selective mutism (typically seen in children aged 4-18), specific phobias, social anxiety disorder and generalized anxiety disorder (affecting both children and adults). Additionally, panic disorder and agoraphobia primarily impact adults, usually beginning around age 18.[1] The World Health Organization (WHO) ranks anxiety disorders as the ninth leading cause of disability worldwide, due to their high occurrence rates, long-term nature and tendency to appear alongside other conditions.[2] These disorders contribute to 3.3% of the global disease burden and are estimated to cost €74 billion across 30 European countries. Despite their widespread impact, treatment rates for anxiety disorders remain insufficient, particularly in low-income nations, though this issue also persists in high-income countries.[3]

CATEGORIES OF ANXIETY DISORDER

Generalized anxiety disorder

GAD is a prevalent psychiatric condition and is among the limited number of anxiety disorders acknowledged in contemporary classification frameworks. The notion of GAD evolved from earlier ideas of 'neurasthenia' and 'anxiety neurosis,' which were introduced in the late 19th and early 20th centuries. GAD was first articulated and distinguished from PD in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) published in 1980. It was subsequently recognized as a separate anxiety disorder in the 10th edition of the International Classification of Diseases (ICD-10) in 1994. The latest versions of these classification systems, namely the DSM-5 from 2013 and the ICD-11 from 2022, continue to include GAD as a diagnosis. Both classification systems outline a comparable array of symptoms. The DSM-5 underscores the presence of excessive anxiety and worry

that is challenging to manage. Additional symptoms associated with GAD include restlessness, muscle tension, difficulties with concentration, the sensation of one's mind going blank, irritability and disturbances in sleep. Conversely, the ICD-11 emphasizes the experience of general apprehensiveness (or 'free-floating anxiety') and excessive worry regarding negative occurrences in various aspects of daily life. Associated symptoms noted in the ICD-11 also include restlessness, muscle tension, sympathetic autonomic overactivity, difficulties in concentration, irritability and sleep disturbances. Both systems stipulate that symptoms must be present for more days than not over a duration of at least six months (according to DSM-5) or several months (as per ICD-11) and must lead to a certain level of functional impairment.

In comparison to healthy individuals, GAD is linked to elevated serum levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol and a diminished response to clonidine treatment suggests heightened α2-adrenoreceptor sensitivity. Additionally, urinary levels of the serotonin metabolite 5-hydroxyindoleacetic acid show a positive correlation with somatic anxiety symptoms. Neuroimaging research on GAD has revealed both structural and functional variations when compared to healthy individuals, although these findings are not uniformly observed. Notable results often include a larger amygdala and a reduced volume of hippocampal gray matter, enhanced connectivity between the amygdala and the prefrontal cortex, as well as heightened amygdala activation in reaction to threatening stimuli.[4]

Panic disorder

Panic disorder is a common mental health issue, impacting approximately 5% of individuals at some stage in their lives. This condition can be profoundly incapacitating, especially when it is accompanied by agoraphobia, leading to significant functional limitations and a diminished quality of life. Additionally, panic disorder imposes a considerable economic strain on both individuals and society, resulting in increased healthcare costs, absenteeism and reduced productivity in the workplace. Certain medical conditions, such as asthma, frequently coexist with panic disorder and lifestyle choices, including smoking, may elevate the risk of its development.

Nevertheless, the exact causal mechanisms remain ambiguous. There are genetic predispositions and early life vulnerabilities that appear to play a role, yet their specific contributions and the underlying pathophysiological processes are not completely elucidated. Although the precise causes of panic disorder are not entirely established, there is substantial evidence indicating the efficacy of various treatment options, including pharmacological approaches and cognitive-behavioral therapies. It is crucial for the public health sector to emphasize the adaptation and broad implementation of these treatment modalities within primary care environments.[5]

Specific phobia

Anxiety disorders rank among the most prevalent mental health issues, yet specific phobias, a subset of these disorders, have not received extensive research attention. Phobias are defined by both fear responses and avoidance behaviors. For those suffering from specific phobias, avoidance can often alleviate the frequency and severity of distress and functional impairment. Nonetheless, these phobias are particularly noteworthy due to their early onset and a pronounced tendency to endure over time. Studies indicate that the lifetime prevalence of specific phobias globally varies between 3% and 15%, with prevalent fears including heights and various animals.

The developmental pattern of phobias generally transitions from initial fear to avoidance, ultimately leading to a formal diagnosis. This progression suggests that intervening at an early stage may help decrease their overall prevalence. Although specific phobias frequently emerge in childhood, their incidence tends to peak during middle and later adulthood. In 10-30% of instances, these phobias can last for several years or even decades and they are closely associated with the emergence of other anxiety, mood and substance use disorders. The significant comorbidity of phobias with other mental health issues, particularly after their onset, implies that early intervention may mitigate the risk of developing additional disorders. Exposure therapy is widely regarded as the primary treatment for specific phobias, although its long-term efficacy may not be as robust as previously believed. This review explores the existing literature concerning the prevalence, incidence, progression, risk factors and treatment options for specific phobias, alongside epidemiological data derived from various population-based studies.[6]

Agarophobia

The authors examine the characteristics of agoraphobia and its various treatment options, dispelling several misconceptions associated with the condition, including those linked to the individual's childhood experiences, sexual development and marital background. They assert that these elements do not enhance the comprehension of agoraphobia. Furthermore, they contest the contemporary notion that agoraphobia is merely a manifestation of endogenous depression. Among the four established psychiatric paradigms medical, behavioral, genetic and psychoanalytic the medical and behavioral approaches currently hold greater prominence, although each framework presents its own set of limitations. The authors contend that the efficacy of behavioral therapies for agoraphobia may not be as universally effective as recent research indicates. While both pharmacological treatment and behavioral therapy have demonstrated positive outcomes, the varying models of agoraphobia lead to inconsistencies in the understanding of the disorder. The authors suggest potential research directions that could aid in reconciling these discrepancies.[7]

Social anxiety disorder

Social anxiety disorder is characterized by an intense fear of social situations in which individuals may face judgment or scrutiny from others. This anxiety typically centers on the worry of being negatively assessed, such as being viewed as anxious, weak, unintelligent, dull or unlikable. The diagnostic criteria for social anxiety disorder, as detailed in the fifth edition of the DSM-5. These criteria have undergone only minor changes since the release of DSM-IV. Social anxiety disorder manifests along a spectrum, incorporating various forms of feared social interactions. Notably, there exists a specific subtype of the disorder that pertains to performance anxiety, often associated with professional contexts such as public speaking, musical performances or presentations in meetings or classrooms. Individuals with this performance-related subtype exhibit distinct differences from those with general social anxiety disorder, including a lower genetic predisposition, a later onset, reduced impairment, heightened physiological responses in performance scenarios and a more favourable reaction to treatment with beta-blockers.[8]

Selective mutism

Selective mutism was first documented in medical literature 140 years ago. The condition gained prominence in adult psychiatry with the introduction of DSM-5, which classified selective mutism in infancy, adolescence and adulthood as a distinct anxiety disorder. Typically, it manifests in early childhood as an inability to speak in specific situations. Diagnosis often occurs only after a child begins school. Frequently, individuals with selective mutism also experience comorbid anxiety disorders, particularly social phobia and depression. The progression of the disorder varies; some individuals may experience a sudden and complete regression of symptoms, while others may see a gradual decline. In some cases, the disorder can persist into adulthood. Previously, a traumatic origin was believed to be the cause, but current understanding suggests a multifactorial etiology involving genetic, psychological and language-related factors. Treatment typically includes psychotherapy, speech therapy and psychopharmacological interventions.[9]

Separation anxiety disorder

In the fifth edition of the DSM-5, separation anxiety disorder is classified as an anxiety disorder, removing the prior limitation that mandated its onset to occur during childhood or adolescence. The lifetime prevalence of this disorder is reported to be 4.8%, with many cases emerging after the age of 18. Despite its significant prevalence, separation anxiety disorder is often underdiagnosed and remains untreated in numerous instances. This narrative review offers a comprehensive overview of the disorder's etiology, clinical characteristics, diagnostic criteria and important differential diagnostic considerations. It also examines prevalent comorbidities and the implications for treatment related to separation anxiety disorder. Furthermore, the review highlights practical considerations for clinical practice and suggests future avenues for treatment and research.[10]

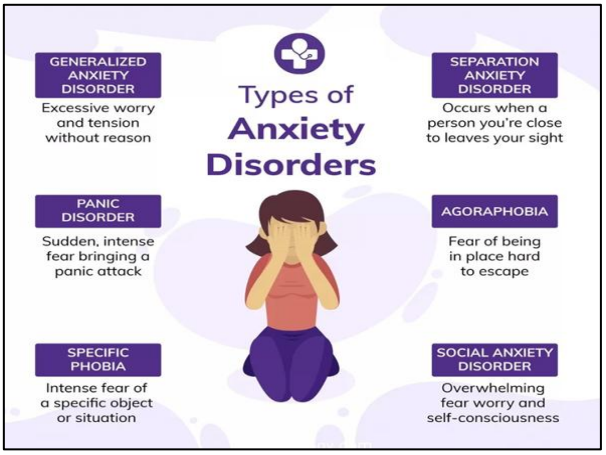

Figure 1: Anxiety disorder.

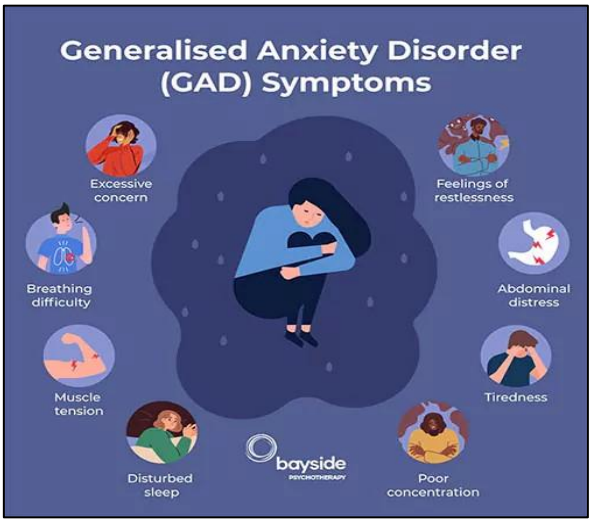

Figure 2: Symptoms of generalized anxiety disorder.

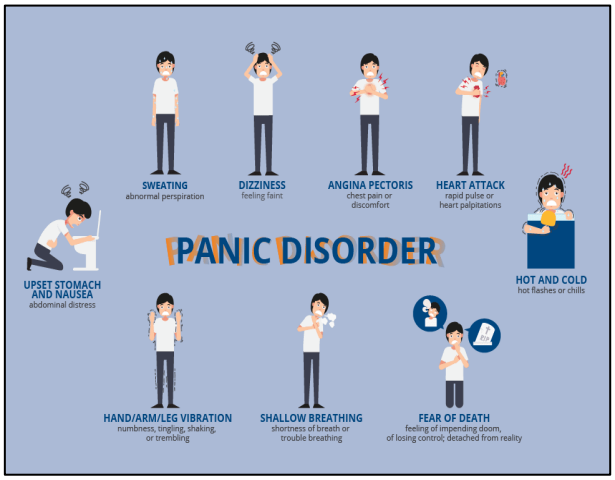

Figure 3: Symptoms of panic disorder.

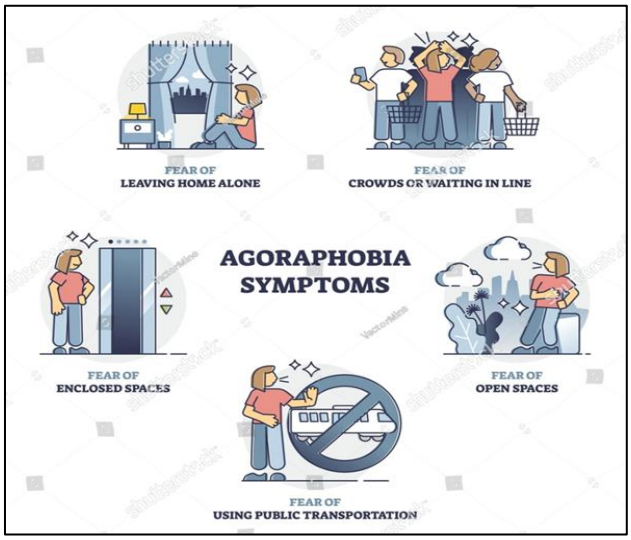

Figure 4: Symptoms of agarophobia.

CLINICAL PRESENTATION

Fear is an emotion that arises in response to a real or perceived threat, whereas anxiety pertains to the expectation of potential future threats, whether they are tangible or not. Both emotions play a crucial role in survival and can be advantageous in various situations. Consequently, experiencing fear and anxiety is common throughout both childhood and adulthood. Clinical intervention may be necessary for fears and anxieties when they are disproportionate to the actual threat, persist over an extended period or disrupt daily activities. Perceived threats can stem from external factors, such as social interactions or health issues, indicating to the individual a sense of danger. Additionally, internal cues, including physical sensations like heart palpitations or difficulty breathing, may also contribute to these feelings. The primary diagnostic frameworks, namely the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the 11th edition of the International Classification of Diseases (ICD-11), categorize anxiety disorders based on similar fundamental symptoms.[11]

Categorical diagnostic criteria serve as valuable tools in clinical practice; however, the distinction between anxiety disorders and normal anxiety often remains ambiguous. Accurately identifying these differences necessitates clinical judgment, which must consider factors such as severity, duration, persistence and, importantly, the degree of distress and impairment experienced by the individual. Symptoms may manifest without leading to distress or impairment, as seen in specific phobias where individuals may never confront the feared object (e.g., snakes). In such instances, medical intervention is generally unwarranted. Conversely, anxiety symptoms and panic attacks can present in milder forms, thereby advocating for the adoption of dimensional approaches rather than strictly categorical methods for diagnosis. For example, isolated panic attacks do not fulfil the criteria for panic disorder as outlined in DSM-5 or ICD-11, nevertheless, these attacks can still disrupt functioning and elevate the risk of developing additional mental health issues. Consequently, panic attacks ought to be regarded as a distinct dimension within the framework of various mental disorders. Symptoms frequently lack the specificity required to differentiate between various anxiety disorders and the occurrence of comorbidity among these disorders is prevalent. Research indicates that between 48% and 68% of adults diagnosed with one anxiety disorder also meet the criteria for another concurrent anxiety disorder. Comorbidity is more frequently observed in clinical environments compared to community settings, as individuals with multiple disorders are more inclined to seek treatment. Furthermore, there is a notable rate of diagnostic instability over time within anxiety disorders, characterized by frequent changes in diagnoses and potential underlying shared causes.[12]

Anxiety disorders represent the most common category of mental health issues in children and are generally the earliest to manifest among various mental illnesses. These disorders often arise during childhood, frequently triggered by factors such as separation anxiety, specific phobias or social anxiety disorder, which leads to their earlier appearance compared to other conditions like depression or substance use disorders. In contrast, disorders such as generalized anxiety disorder, agoraphobia and panic disorder exhibit a wider range of onset ages and may occasionally emerge later in life.[13]

Understanding the cognitive and behavioural patterns linked to anxiety can assist in pinpointing the most probable diagnoses. For instance, a tendency to avoid social interactions may indicate separation anxiety (if the primary concern is the fear of losing attachment), panic disorder (if the apprehension revolves around experiencing panic attacks), social anxiety disorder (if the fear pertains to being evaluated by others) or agoraphobia (if the fear is related to feeling confined).[14]

DETECTION AND DIAGNOSTIC METHODS

Anxiety disorders are often inadequately diagnosed across different healthcare environments, making it essential for healthcare professionals to monitor their prevalence. This is especially vital as individuals suffering from anxiety disorders may exhibit symptoms that are not readily identified as being related to anxiety. For instance, patients experiencing panic disorder may seek treatment in general or emergency care settings, where their symptoms could be incorrectly linked to cardiac or respiratory conditions.[15] It is essential for clinicians to recognize anxiety disorders, as the majority of individuals affected by these conditions receive treatment in primary care settings. This awareness enables them to deliver appropriate care or refer patients to specialists when required.[16]

The absence of blood tests, genetic markers or imaging techniques for diagnosing anxiety disorders necessitates that the diagnosis be based on a comprehensive mental

health history and thorough examinations, which must be diligently overseen by all primary care providers. Utilizing structured or semi-structured clinical interviews, such as the Composite International Diagnostic Interview aligned with DSM-5 or ICD-11 criteria or the Structured Clinical Interview for DSM Disorders, can facilitate an accurate diagnosis. In the case of children, assessments like the Kiddie-SADS necessitate further contributions from parents or caregivers.[17]

Clinicians can utilize rating scales, such as the Hamilton Anxiety Scale, to evaluate the severity of anxiety disorders and track patient progress. Additionally, validated self-report instruments like the Beck Anxiety Inventory are beneficial for assessing particular anxiety symptoms, including those related to panic disorder. Nevertheless, although anxiety screening across different environments is crucial, its overall effectiveness and cost-effectiveness remain to be thoroughly determined.[18]

SYMPTOMS

Physical symptoms include

Heart rate

Increased heart rate, palpitations or a rapid heartbeat.

Breathing

Rapid breathing (hyperventilation) or difficulty in breathing.

Sweating

Excessive sweating, shakiness or trembling.

Nausea

Experiencing feelings of nausea or sickness.

Light headedness

Feeling faint, pale or dizzy

Mental symptoms include

Worry

Experiencing stress or anxiety, accompanied by anxious thoughts or beliefs.

Irritability

Exhibiting signs of irritability, tension or restlessness.

Difficulty concentrating

Struggling to focus or make decisions.

Low mood

Experiencing feelings of sadness or depression.

Behavioural symptoms involve

Avoidance

Steering clear of situations that provoke anxiety or panic.

Panic attacks

Encountering sudden episodes of intense anxiety and fear or harbouring a fear of experiencing panic attacks.

Causes

The exact causes of anxiety disorders are not completely understood. However, life experiences, such as traumatic events, may trigger anxiety disorders in individuals who are already susceptible to anxiety. Inherited traits can also play a role.

Medical causes

For certain individuals, anxiety could be related to an underlying health condition. In some instances, the symptoms of anxiety may be the initial signs of a medical issue. If your doctor believes your anxiety may have a medical origin, they may recommend tests to check for any potential health problems.

Examples of medical problems that can be linked to anxiety include heart disease, diabetes, thyroid problems, such as hyperthyroidism, respiratory disorders, such as COPD and asthma, drug misuse or withdrawal, withdrawal from alcohol, anti-anxiety medications (benzodiazepines) or other medications, chronic pain or irritable bowel syndrome, rare tumors that produce certain fight-or-flight hormones, sometimes anxiety can be a side effect of certain medications too.

Risk factors

Several factors may elevate the risk of developing an anxiety disorder.

Trauma

Individuals, particularly children, who have endured abuse, trauma or have been witnesses to traumatic incidents are at a heightened risk of developing anxiety disorders in later life. Similarly, adults who experience traumatic events may also be susceptible to these disorders.

Health-related stress

The presence of a health condition or serious illness can generate considerable anxiety regarding treatment options

and future health outcomes, thereby increasing the likelihood of anxiety disorders.

Cumulative stress

Experiencing a significant life event or a succession of minor stressors can lead to intense anxiety. Examples include the death of a loved one, workplace pressures or persistent financial difficulties.

Personality characteristics

Certain personality traits may predispose individuals to the development of anxiety disorders.

Coexisting mental health issues

Those who suffer from other mental health conditions, such as depression, are more prone to also experience anxiety disorders.

Genetic predisposition

Anxiety disorders often have a familial component, meaning that having close relatives with such disorders can heighten an individual's risk.

Substance use

The consumption, misuse or withdrawal from drugs or alcohol can exacerbate or contribute to anxiety symptoms.

Traditional therapy for anxiety

Complementary and alternative medicine (CAM) therapies include a variety of practices that exist outside the realm of conventional medicine. These practices encompass herbal remedies, massage therapy, acupuncture, yoga, tai chi, meditation, qigong, mindfulness relaxation techniques, among others. CAM therapies are frequently perceived as more natural and safer options for managing prevalent health concerns when compared to traditional medical approaches. In recent years, there has been a notable increase in the global acceptance and utilization of CAM therapies.

There is an increasing body of evidence that supports the efficacy of certain CAM) therapies in addressing mental health issues, particularly anxiety disorders. Research conducted by Yang XY et al, indicates that acupuncture, when utilized to alleviate anxiety in individuals with generalized anxiety disorder (GAD), has yielded favourable outcomes in comparison to a control group. Yoga, recognized as a widely accepted and safe therapeutic practice, incorporates a blend of physical postures, breathing techniques, relaxation, meditation and mindfulness and has been identified as an effective intervention for GAD. Systematic reviews further suggest that herbal medicine may be a promising option for treating GAD with a lower incidence of adverse effects. A waiting-list control study revealed significant clinical improvements associated with mindfulness therapy in reducing anxiety symptoms. Moreover, meta-analyses have demonstrated that Tai Chi interventions can positively influence various mental health indicators, including anxiety, stress and emotional disorders, across diverse populations.[19]

The relative effectiveness of different CAM therapies is still not well established. In contrast to conventional pairwise meta-analysis, NMA allows for the integration of effect sizes from numerous studies that evaluate multiple interventions or treatments through indirect comparisons. Consequently, this study aims to evaluate the efficacy differences among various CAM therapies, intending to offer significant insights that can aid in clinical decision-making.[20]

EMERGING DRUGS FOR THE TREATMENT OF ANXIETY

Considerable advancements have been achieved in neurobiological research focused on elucidating the molecular and neurocircuit alterations associated with anxiety. Fundamental studies have yielded important insights into the mechanisms that regulate fear responses in animals, leading to the creation of various animal models for the screening of anxiolytic agents. However, despite these developments, there have been no fundamentally novel treatments for anxiety introduced in the past twenty years. The applicability of existing animal models for human anxiety disorders is still limited, presenting a significant challenge for drug development in this area. For a comprehensive examination of animal models of anxiety and their effectiveness.[21]

There is a pressing requirement for novel and more efficient therapies for anxiety. As previously noted, anxiety disorders are associated with considerable functional limitations and a significant burden on both patients and their families.[22,23] These conditions lead to higher healthcare usage and a reduction in work efficiency.[24,25] Existing treatment options fail to sufficiently meet the public health requirements linked to these conditions. For example, recent extensive meta-analyses have not been able to validate the effectiveness of benzodiazepines or azapirones, such as buspirone, in the treatment of panic disorder.[26,27] PTSD, GAD and SAD exhibit only a limited response to current treatment options, such as SSRIs.[28,29] A concerning report from the Institute of Medicine determined that there is inadequate evidence to substantiate the efficacy of SSRIs or other pharmacological treatments in the management of PTSD.[30] There is a notable and substantial demand for the development of new pharmacological therapies to address anxiety disorders.

Existing treatment

Currently, the agents that have received approval from the US FDA for the management of anxiety disorders are

outlined in Table 1. A substantial body of randomized controlled trials (RCTs) demonstrates the efficacy of SSRIs and SNRIs as primary treatment options for GAD, SAD, panic disorder and post-traumatic stress disorder (PTSD). A review encompassing 12 RCTs focused on panic disorder revealed a mean effect size of 0.55 for SSRIs in comparison to placebo. In the case of GAD, the response rates for SSRIs generally fall between 60% and 75% in RCTs, whereas placebo response rates typically range from 40% to 60%. Furthermore, evidence indicates that PTSD may exhibit a lower responsiveness to existing pharmacological treatments relative to other anxiety disorders. A Cochrane review analyzing 35 RCTs with a total of 4,597 participants endorsed the use of SSRIs as the first-line pharmacotherapy for PTSD.[31-33]

NEUROTRANSMITTERS AND THEIR RELATED MEDICINE IN ANXIETY

Serotionin

Vortioxetine

Vortioxetine is a serotonergic medication developed by Lundbeck, which has received approval from both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the management of Major Depressive Disorder (MDD). Its primary mechanism of action is as a serotonin transporter (SERT) inhibitor; however, it also possesses several additional pharmacological properties. These include functioning as a full agonist at the 5-HT1A receptor, a partial agonist at the 5-HT1B receptor and an antagonist at the 5-HT1D, 5-HT3 and 5-HT7 receptors. By inhibiting SERT, vortioxetine elevates the extracellular concentrations of serotonin, dopamine, noradrenaline, acetylcholine and histamine in regions such as the ventral hippocampus and prefrontal cortex (PFC). Furthermore, preclinical studies indicate that it also influences GABA and glutamate neurotransmission.[34]

Three distinct RCTs have been carried out to evaluate the effectiveness of vortioxetine in treating GAD, yielding varied outcomes.[35] In a particular study, individuals diagnosed with GAD received treatment with vortioxetine at a dosage of 5 mg daily over a period of 8 weeks (n=150), while a control group was administered a placebo (n=151).

The results indicated that the group receiving vortioxetine experienced a significantly greater decrease in the total Hamilton Anxiety Rating Scale (HAM-A) score, with a reduction of -14.30 compared to -10.49 in the placebo group ($p<0.001$). Nevertheless, two additional randomized controlled trials (RCTs) focusing on GAD yielded negative outcomes. The vortioxetine group commonly reported side effects such as nausea, headache, dizziness and dry mouth. In summary, the clinical evidence points to a possible advantage of vortioxetine in the treatment of GAD; however, further research is necessary to validate these results.[36]

Vilazodone

Vilazodone, which was developed by Merck, received approval from the U.S. Food and Drug Administration (FDA) in 2011 for the management of Major Depressive Disorder (MDD). Besides acting as a selective serotonin reuptake inhibitor (SSRI), vilazodone also serves as a partial agonist at the 5-HT1A receptor, akin to the mechanism of buspirone.[37] Preclinical research indicates that the stimulation of presynaptic 5-HT1A autoreceptors may postpone the emergence of the antidepressant and anxiolytic effects commonly associated with SSRIs.

By concurrently inhibiting serotonin reuptake and activating the 5-HT1A receptor, vilazodone has the potential to mitigate this delay.[38] This dual mechanism of action may enhance the antidepressant effect, minimize the side effects linked to serotonin reuptake inhibition and help alleviate symptoms of anxiety. Nevertheless, the clinical relevance of this pharmacodynamic profile is still unclear. Currently, there have been no published RCTs that have specifically investigated the effects of vilazodone in individuals diagnosed with anxiety disorders.[39] A subsequent analysis of two Phase III randomized controlled trials involving patients with MDD indicated that vilazodone may be beneficial for those experiencing MDD with anxious features.

After an 8-week treatment period, individuals in the active treatment cohort exhibited notable improvements in both somatic and psychological anxiety symptoms when compared to the placebo cohort. Preliminary data also imply that vilazodone could be linked to a reduced occurrence of sexual dysfunction relative to other selective serotonin reuptake inhibitors (SSRIs); however, additional studies are required to validate this finding. In conclusion, further investigation is essential to comprehensively evaluate the efficacy of vilazodone in the treatment of anxiety disorders.[40]

Melatonin

Agomelatine

Agomelatine is a distinctive medication that functions as an agonist at the melatonin receptors (MT1, MT2) while simultaneously acting as an antagonist at the 5-HT2C receptor. It has received approval for the treatment of major depressive disorder (MDD) in Europe; however, it has not yet been authorized for use in the United States.[41] Research at the molecular and cellular levels indicates that agomelatine's synergistic impact on the melatonin and serotonin systems may facilitate neuroplasticity, which includes the enhancement of neurogenesis within the adult hippocampus.[42] Preclinical research indicates that agomelatine has the potential to mitigate stress-related elevations in glutamate release within the prefrontal cortex (PFC) and may assist in the synchronization of circadian rhythms by activating melatonergic and serotonergic receptors located in the suprachiasmatic nucleus (SCN) of

the hypothalamus. Although there are similarities between the neural effects of agomelatine and those of conventional antidepressants, the extent to which the drug's distinct molecular actions influence its overall mechanism of action remains uncertain.[43] Two RCTs have been performed to assess the efficacy of agomelatine in individuals diagnosed with GAD. In a Phase III, 12-week, three-arm RCT that included escitalopram as an active comparator, agomelatine demonstrated a significant reduction in Hamilton Anxiety Rating Scale (HAM-A) scores when compared to placebo.[44] The effectiveness of escitalopram and agomelatine was determined to be comparable. In a subsequent RCT, which consisted of a 42 weeks open-label phase (25–50 mg/day) followed by a six-month double-blind phase, the group receiving agomelatine exhibited a notably lower relapse rate in comparison to the placebo group (19.5% versus 30.7%, p=0.045).

Furthermore, a meta-analysis encompassing six RCTs involving patients with MDD and concurrent anxiety symptoms corroborates the effectiveness of agomelatine in alleviating anxiety.[45] Several case reports and open-label trials have indicated the possible advantages of enhancing treatment for obsessive-compulsive disorder (OCD) with agomelatine. The findings from a recent Phase II trial examining the efficacy of agomelatine for OCD remain unpublished (NCT01108393).[46]

Norepinephrine and dopamine

Noradrenergic hyperactivity has been recognized as a significant contributor to the stress response, with irregular noradrenergic signalling consistently linked to behaviors associated with anxiety.[47] Elevated catecholamine activity in response to stress, which may impair the functioning of the prefrontal cortex (PFC), has been associated with post-traumatic stress disorder (PTSD) and various anxiety disorders, as evidenced by both clinical and preclinical studies.[48] Research indicates that individuals with PTSD exhibit markedly elevated levels of norepinephrine in their cerebrospinal fluid (CSF) when compared to healthy control subjects.[49] Translational research indicates that inhibiting the α-1 receptor and/or stimulating the α-2 receptor could serve as effective pharmacological approaches for the treatment of PTSD and various anxiety disorders.[50]

Guanfacine

Guanfacine is an α-2 adrenergic receptor agonist that has received approval in an extended-release formulation for the management of attention deficit hyperactivity disorder (ADHD). Its action as an agonist at α-2 presynaptic auto-receptors contributes to the reduction of atypical noradrenergic signalling, which is believed to alleviate symptoms associated with anxiety and trauma.[51] Two small double-blind RCTs have failed to demonstrate conclusive evidence regarding the efficacy of guanfacine in reducing PTSD symptoms in adults. Conversely, open-label studies indicate that the medication may be beneficial in addressing PTSD symptoms and related nightmares in children and adolescents. At present, there are no RCTs investigating the application of guanfacine for other anxiety disorders.[52] Current clinical trial data does not demonstrate its efficacy in treating PTSD; however, ongoing research is exploring its potential benefits for other anxiety disorders, such as GAD, social phobia and SAD (NCT01470469).[53]

Nepicast

Nepicast functions as a selective inhibitor of dopamine β-hydroxylase (DBH) and is currently under investigation as a potential therapeutic option for post-traumatic stress disorder (PTSD) (NCT00659230, NCT00641511). By inhibiting β-hydroxylase, nepicast diminishes the conversion of dopamine into norepinephrine, which in turn reduces noradrenergic signalling at synaptic junctions. Importantly, studies conducted on animals have indicated that this medication may effectively mitigate behaviors associated with cocaine and alcohol use. Nevertheless, further research is essential to ascertain the potential of this drug class in the treatment of PTSD and other anxiety-related disorders.[54]

Anti-anxiety drugs used in treatment of anxiety

Anti-anxiety medications are utilized to alleviate the symptoms associated with various anxiety disorders, including GAD, panic disorder, social anxiety disorder and PTSD. The primary objective of these medications is to diminish the severity of anxiety and stress, thereby assisting individuals in restoring their functionality and overall well-being. The ways in which anti-anxiety drugs operate can differ markedly based on their specific class. This document examines the mechanisms of action for several prominent categories of anti-anxiety medications.

Benzodiazepines

Benzodiazepines, recognized as the quintessential anxiolytics, were first introduced in the early 1960s and rapidly gained widespread acceptance for numerous reasons. The primary factor behind their popularity was the societal demand for substances that provide calming effects. Historically, this demand has predominantly been satisfied through the use of alcohol. In the decade leading up to the advent of benzodiazepines, barbiturates and meprobamate were frequently employed to mitigate anxiety and distress.

However, growing concerns regarding the potential for benzodiazepine dependence facilitated the promotion of newer antidepressants for treating anxiety disorders. Consequently, by the late 1990s, most clinical guidelines favoured SSRIs and SNRIs as the preferred pharmacological options for anxiety disorders. The enduring popularity of benzodiazepines can be attributed to several factors, including their reliable efficacy in

alleviating anxiety, tension and various physical manifestations of anxiety; rapid onset of therapeutic effects; relatively favorable tolerability; the option for administration on an 'as-needed' basis; and a comparatively safe profile in cases of overdose. Additionally, challenges associated with antidepressants in managing anxiety disorders have further enhanced the appeal of benzodiazepines.[55]

Benzodiazepines (BZDs) are primarily utilized for the treatment of panic disorder and GAD in relation to anxiety management. Specifically, temazepam is frequently prescribed for insomnia, clonazepam is often indicated for anxiety and seizure control, lorazepam is utilized for catatonia and seizure termination when administered intramuscularly or intravenously and diazepam is commonly used for anxiety, muscle spasms and rectal administration for seizures. In the context of anxiety, BZDs serve as a temporary solution while initiating other medications or as immediate relief for panic attacks. Due to concerns regarding dependence and withdrawal, SSRIs and antidepressants have become the primary treatment options for these disorders. Nevertheless, owing to their delayed therapeutic effects, BZDs remain widely prescribed for these conditions.[56]

Selective serotonin re-uptake inhibitors

Anxiety disorders, including GAD, SAD and panic disorder, rank among the most prevalent psychiatric conditions. SSRIs are currently regarded as the first-line pharmacological treatment for these disorders, supported by extensive research demonstrating their safety and efficacy. In comparison to alternative anxiolytic medications, SSRIs tend to have a more favourable side effect profile and also address depression, which frequently co-occurs with anxiety disorders. A meta-analysis encompassing 57 clinical trials has validated the effectiveness of SSRIs in treating anxiety disorders, indicating that higher doses within the therapeutic range correlate with more significant improvements in symptoms.[57]

The SSRIs, following their effective and widespread application in treating depression, are increasingly being recognized as first-line treatments for anxiety disorders. Currently, SSRIs are approved for managing panic disorder and OCD and they have also shown efficacy in addressing social phobia, PTSD and GAD. The growing clinical acceptance of SSRIs for anxiety treatment can be attributed to their comparable or superior effectiveness relative to traditional tricyclics and benzodiazepines, along with a more favourable side effect profile.

Given that individuals with anxiety disorders often report a higher incidence of side effects and greater distress from them compared to those with other psychiatric conditions, SSRIs offer a notable benefit for both patients and healthcare providers. While the effectiveness of SSRIs in treating anxiety disorders is becoming increasingly recognized, the precise mechanisms by which they alter the pathophysiological and emotional manifestations of anxiety across various disorders remain to be fully understood.[58]

Serotonin-norepinephrine reuptake inhibitors

SNRIs specifically target the reuptake of norepinephrine and serotonin, demonstrating effectiveness and general tolerability as treatment options for individuals with anxiety disorders. They may offer certain clinical benefits compared to selective serotonin reuptake inhibitors (SSRIs), which are widely regarded as the primary pharmacological treatments for these conditions. Anxiety disorders often exhibit a chronic nature, high comorbidity rates and a tendency for partial responses to conventional therapies. The rising utilization of SNRIs indicates a response to existing clinical gaps related to overall efficacy, remission rates and the tolerability of treatments.[59]

Buspirone

Buspirone is classified as an anxiolytic medication. Initially developed as an antipsychotic, it was ultimately deemed ineffective for treating psychosis; however, it was recognized for its beneficial anxiolytic properties. Recently, buspirone has gained popularity, largely due to its favourable side-effect profile in comparison to other anxiolytic options. It is primarily indicated for the treatment of GAD and is approved by the United States Food and Drug Administration for managing anxiety disorders and providing short-term relief from anxiety symptoms. Additionally, buspirone is sometimes utilized off-label to augment treatment in cases of unipolar depression. The drug's effectiveness has been validated through controlled clinical trials involving outpatients diagnosed with GAD.

Typically, buspirone is employed as a second-line treatment following selective SSRIs when patients either do not respond to SSRIs or experience intolerable side effects. Furthermore, it has been used to mitigate the sexual side effects associated with SSRIs. Unlike benzodiazepines and barbiturates, buspirone does not carry a risk of physical dependence or withdrawal, as it does not interact with GABA receptors. However, it is important to note that buspirone is not effective as an acute anxiolytic, with its therapeutic effects generally taking 2 to 4 weeks to manifest. Its efficacy in treating GAD is comparable to that of benzodiazepines and it is noteworthy that buspirone has minimal sexual side effects, even demonstrating the ability to alleviate the adverse sexual effects of SSRIs when used as an adjunct therapy.[60]

Beta-blockers

Beta-adrenergic receptor antagonists have introduced a novel approach for investigating the biological underpinnings of anxiety and for managing individuals

with anxiety disorders. These receptors play a crucial role in mediating sympathetic responses that influence the heart's contraction rate and strength, bronchial muscle tone, blood flow to skeletal muscles, gastrointestinal motility and bladder function. When stimulated by epinephrine or beta-agonists like isoproterenol, these receptors can elicit anxiety symptoms in those with anxiety disorders. Conversely, the administration of beta-blockers, such as propranolol, can mitigate the sympathetic-induced tachycardia and other physiological signs associated with anxiety. Although there remains some ambiguity regarding their precise mechanism of action and their comparative efficacy relative to other anxiolytic medications, beta-blockers are generally considered to be safer alternatives to benzodiazepines in the treatment of anxiety.[61]

Alpha-2 adrenergic agonists

Noradrenergic alpha-2 receptor agonists are employed to reduce noradrenergic activity when utilized as antihypertensive agents. Notably, these medications are also prescribed for patients with PTSD and various psychiatric conditions to alleviate agitation. This class of drugs may serve as a nonaddictive, off-label alternative to benzodiazepines for managing agitation, hyperarousal and insomnia linked to PTSD. Meanwhile, noradrenergic alpha-1 receptor antagonists have gained significant traction, supported by an increasing body of evidence and more frequent clinical application in the treatment of PTSD-related nightmares. Clonidine and guanfacine, both alpha-2 receptor agonists, activate postsynaptic adrenergic autoreceptors, leading to a reduction in sympathetic nervous system outflow from the central nervous system. Although there are no direct studies comparing the side effects of alpha-2 receptor agonists with those of benzodiazepines and atypical antipsychotics, alpha-2 receptor agonists appear to be safer, as they do not result in permanent movement disorders, metabolic syndrome or the potential for dependence or addiction.[62]

Antipsychotics

Antipsychotics constitute a category of medications that have garnered significant attention for their application in non-psychotic disorders over the years. The first-generation antipsychotics (FGAs), often referred to as "typical" antipsychotics, were initially utilized primarily for the treatment of schizophrenia, but their use extended to conditions such as bipolar mania, agitation (both psychotic and non-psychotic), sleep disorders and Tourette's syndrome. Notably, trifluoperazine received approval from the US FDA in 2001 for the treatment of non-psychotic anxiety. Research involving both inpatients and outpatients in academic environments indicates that the prescription of antipsychotics for anxiety and related disorders is prevalent.

Canadian clinical guidelines suggest that antipsychotics should be considered only as a third-line treatment or as an adjunctive therapy for anxiety disorders, with options including olanzapine, quetiapine, risperidone or aripiprazole, contingent upon the specific anxiety disorder. Evidence supporting the use of second-generation antipsychotics (SGAs) in panic disorder (PD) is limited or lacking. Despite the lack of formal approval, antipsychotics are frequently prescribed off-label for various conditions, including insomnia and anxiety. There appears to be a growing trend in the use of antipsychotics for anxiety, particularly in patients who have not responded to first- or second-line treatment options.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) Guidelines endorse the use of SGAs for the treatment of bipolar disorder and primarily as adjunctive therapy for major depressive disorder (MDD). Consequently, patients with anxiety disorders who also have comorbid bipolar disorder or MDD are likely to be prescribed SGAs in accordance with these guidelines. Furthermore, the assumption that medications effective for MDD may also benefit anxiety disorders can lead to an increase in the prescription of SGAs for patients experiencing anxiety.[63]

CONCLUSION

Pharmacological advancements in the management of anxiety are transforming the array of treatment options available to individuals affected by anxiety disorders. While conventional therapies, including benzodiazepines, SSRIs and SNRIs, remain essential for alleviating symptoms, particularly in cases of acute and chronic anxiety, their inherent limitations such as adverse effects, potential for dependency and delayed therapeutic onset have spurred the exploration of innovative treatments aimed at overcoming these challenges. Newly emerging therapies, including ketamine, buspirone, cannabinoids and psychedelic-assisted therapy, present unique mechanisms of action and have demonstrated encouraging results in clinical studies. Additionally, recent investigations into neurosteroids and the gut-brain axis indicate that future anxiety treatments may become increasingly tailored and personalized. As these novel therapies progress through clinical validation, there is optimism that patients will gain access to more effective, safer and rapidly acting options for anxiety management.

The pharmacological approach to anxiety is shifting towards a more individualized strategy, integrating both established and novel therapies. With advancements in our understanding of neurobiology, it is anticipated that new treatment modalities will arise, providing hope for those whose anxiety proves resistant to traditional interventions. Nonetheless, further research is essential to comprehensively assess the safety, efficacy and long-term effects of these emerging therapies prior to their widespread adoption in clinical settings.

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