IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

NOVEL PHARMACOLOGICAL TARGETS IN DRUG DEVELOPMENT FOR THE TREATMENT OF ANXIETY AND ANXIETY-RELATED DISORDERS

Anjali Kumari*, Anil Kumar[1], Kapil Kumar Verma[2]
[1] Student, [2]Assistant Professor, [3]Principal
Minerva College of Pharmacy
[1]Himachal Pradesh Technical University, Kangra, India

Abstract ; Anxiety disorders contribute heavily to the global burden of disease and are associated with considerable functional impairment. For many people, these can provide relief though not all respond and the limitations of benzodiazepines (addiction, sedation) or selective serotonin reuptake inhibitors (SSRIs; side effects like sexual dysfunction or weight gain) mean there is a substantial proportion who continues to suffer. The present paper is a narrative-review of the new pharmacological targets in recent drug development for Anxiety and Anxiety-Related Pathologies. In this review, we emphasis possible innovative strategies (modulation of the inhibitory GABAergic system, neuropeptide such as oxytocin and vasopressin, glutamatergic signaling pathways and interactions with the endocanabinoid system). Moreover, the therapeutic opportunities provided by psychedelics and its relationship to neuroinflammation are also discussed. Through the lens of a model preventing mechanism given as example, considerations for future treatments could involve targeting these mechanisms more directly leading to better and tailored interventions capable of addressing some long standing issues in anxiety disorder individuals. Biomarker-guided strategies in cancer

Keywords: Anxiety disorders, pharmacological targets, GABAergic system, neuropeptide, glutamatergic pathways, endocannabinoid signaling, psychedelics, neuroinflammation, drug development

INTRODUCTION

Anxiety is a negative emotional reaction to potential threats or dangers, and it can lead to negative affective symptoms, behavioral symptoms, and thought distortion. The International Statistical Classification of Diseases and Related Health Problems (ICD-10) currently classifies anxiety disorders into generation based on clinical observation criteria. This analysis looks into the often disregarded risks associated with the misuse of gabapentin and pregabalin, with a focus on mortality outcomes over a two-year period. Hydroxazine for generalized anxiety. D-cycloserine and performance under various anxiety states in volunteers. The role of anticonvulsant drugs in anxiety disorders. Antiepileptic drugs in the treatment of anxiety disorder. Fifty years of

obstacles and hope in the anxiolytic drug discovery(15). " Clonidine's effects on anxiety disorders "A pooled analysis of three vilazodone trials was used to characterize sexual function in patients with generalized anxiety disorder."Gepirone and the treatment of panic disorder: an open study" . A new antidepressant with 5-HT1A agonistic qualities is gepirone hydrochloride. D-cycloserine augmentation of exposure therapy for social anxiety disorder. A randomized clinical experiment examined the timing of D-cycloserine doses to enhance exposure therapy for social anxiety disorder. An analysis of various methods for treating dental anxiety in adults. Alpha5IA, a GABA-A receptor alpha5 subtype-selective inverse agonist,: preclinical and clinical pharmacology. Substance P: A neuropeptide implicated in the anxiety disorders' psychopathology. Results from 4 randomized, double-blind, placebo-controlled studies on the use of the vasopressin V1b receptor antagonist SSR149415 in the treatment of major depressive and generalized anxiety disorders. The function of the neuropeptide cholecystokinin in the neural network of panic disorder (. Endogenous modulators of anxiety: neuroactive steroids. The use of neurosteroids as neuromodulators in anxiety disorder treatment . A systematic review and meta-analysis of the use of cannabinoids to treat mental illnesses and their symptoms. One possible treatment for anxiety disorders is cannabidiol. Patients with treatment-naive social phobia experience less anxiety when they are simulated to speak in public thanks to cannabidiol. A systematic review and meta-analysis of the use of cannabinoids to treat mental illnesses and their symptoms. One possible treatment for anxiety disorders is cannabidiol. Patients with treatment-naive social phobia experience less anxiety when they Cannabidiol. 8A comprehensive analysis of clinical trials examining the safety and efficacy of kava kava in the treatment of anxiety symptoms. Current research on kava for generalized anxiety disorder is reviewed. Supplementing with saffron and its impact on anxiety and depression symptoms: a comprehensive review and meta-analysis. Lamotrigine dosage for agoraphobia and panic disorder. Clinical practice recommendations for anxiety, PTSD, and OCD in Canada. Treatment guidelines for those suffering from panic disorder. In the development of medications to treat anxiety and illnesses connected to anxiety, novel pharmacological targets are being explored. A network meta-analysis comparing the tolerability and comparative effectiveness of first-line medications for the acute treatment of generalized anxiety disorder in adults. A meta-analysis comparing the efficacy of SSRIs and TCAs in treating panic disorder.A meta-analysis and systematic review were conducted on Propranolol use in treating anxiety disorders.

Figure 1: Anxiety

Figure 2: Symptoms of anxiety

Anxiety Disorders in Children: Overview

Anxiety disorders are common in children, with prevalence estimates between 5.7% and 17.7%. The DSM-IV-TR identifies several anxiety disorders in children, including separation anxiety disorder, generalized anxiety disorder, social phobia, specific phobia, obsessive-compulsive disorder, and posttraumatic stress disorder.

Generalized anxiety, separation anxiety, and specific phobias are the most frequently diagnosed, affecting about 5% of youth.

Cognitive Distortions and Processing Abnormalities

Kendall's theory suggests that anxiety in children stems from overly active cognitive schemas focused on danger. Cognitive distortions, such as attentional bias (where anxious children pay more attention to threatening information) and interpretational bias (where they view ambiguous situations negatively), play a significant role in this anxiety.

Research using tasks like the dot probe has shown that anxious children react more quickly to threatening words compared to neutral ones. Additionally, studies indicate that anxious children interpret ambiguous situations as threatening more often than their nonanxious peers.Daleiden and Vasey (1997) proposed that anxious children might also process information differently by quickly jumping to conclusions about threats, often ignoring additional context that could alleviate their fears. For example, a dog on a leash may be seen as dangerous by a child with a phobia, even if the situation is not threatening.

Key Studies and Findings

Several studies support these ideas:

Muris et al. (2000c) found that children with high social anxiety detected threats earlier and perceived more danger in ambiguous stories. In follow-up studies, it was shown that threat perception abnormalities were present not only in social situations but across various contexts. Overall, evidence suggests that anxious children exhibit consistent patterns of threat perception distortions, indicating a heightened sense of danger.

The Role of Anxiety Types

While high general anxiety levels predict these distortions, the specific roles of state anxiety (anxiety in response to immediate situations) have not been fully explored in children. Research in adults suggests that both general and state anxiety influence cognitive distortions. To further investigate this, a current study aims to determine how general and state anxiety contribute to threat perception abnormalities in children aged 8–13. Children will complete self-report measures of anxiety before undergoing an interview using ambiguous stories to assess their threat perception.

Hypotheses

The study hypothesizes that:

1. High general anxiety will correlate with threat perception abnormalities.

2. State anxiety may influence these abnormalities, or there may be an interaction between general and state anxiety (1).

Symptoms of Anxiety:

Conceptualizing Anxiety

Anxiety is a word that gets thrown around with very little actually understanding what it means or whats involved. You have heard a friend, partner, colleague or maybe yourself saying: «I suffer from anxiety» OR «I am such an anxious person»?«OR. I worry to much». What does he really mean when people use those statements? Do they understand that there is such a thing as healthy normal anxiety? They have a mental illness? or are they Split-affluent?? Self-diagnosed? Do they even know that there are multiple types of anxiety? Do they mean fear not anxiety? As a mental health provider, you may have to evaluate and distinguish an anxiety disorder if present from one or more of the others. Dont worry about it, later on this module we'll get back into the different forms of anxiety disorders. Anxiety is well-describable by the multiple definitions it possesses and within those differences, there can be overlap. Before you read the next statement, what would be your definition of anxiety? I give you an example with the definition used by The American Psychological Association (APA). Anxiety is an emotion (APA, 2022) that includes feelings of tension, worried thoughts and increased blood pressure among other physical changes. Individuals suffering from anxiety disorders tend to experience repetitive, obsessive thinking. They may even shy away from certain scenarios because of the fear. They can also experience physical symptoms like sweating, shaking, dizziness or a fast heart rate.

Continuing on the subject of anxiety, you may wonder to yourself what separates out-and-out anxiety from stress and fear. While there is some overlap between these two emotional responses, they come with rather different features. The key differences include stress 1) typically having trigger in the environment (i.e. school or work project deadline) (APA, 2022). Once the external trigger goes away, stress symptoms are likely to disappear. But if stress continues for a long time, such constant exposure can weaken the body and cause anxiety symptoms to emerge; sometimes it even reaches up disordered levels of anxiety. Chronic stress and anxiety like that can actually cause a stress response. When the stress response goes on activities specific areas of your brain to flood with hormones in order for you getting safety (cortisol, adrenalin). Second, anxiety is typically activated by an inside trigger which might incorporate physical sensations, stress reaction/fear

response or considerations (known as cognitions). Shortness of breath, or feeling ‘guarded’ Panic and/or anxiety In contrast, when we view an event in a biased or irrational way (i.e.: have distorted thinking), it leads to more negative emotions and symptoms that often remain even after the real trigger is gone(Heshmet, 2018). For the third emotion, fear happens when there is an impending danger (real and perceived). Fear, as you know is very present tense oriented. Negative stimuli (e.g. threat, challenge etc.) that are likely to happen in the future or at any time are cause anxiety response as an emotional reaction; on the other hand(Heshmet, 2018). For instance, someone who is hesitant may get over active anxiety and worry needlessly about a bio course test next week or if they are terrified of needles — the fact that at some point in time they will have to go through a surgery. Situational: an x race again and you … may not do well —> anticipation = anxiety As per American Psychiatric Association, et al., (2013), pages. “States use all or nothing medications; these two states are similar but they overlap and also differ. Fear: More often conceived as accompanied by surges of arousal (which we have already described) necessary for fight/flight/freeze responses, thoughts and awareness of immediate danger, the motivation/action to escape in response. Anxiety associated with still a lot more muscle tension vs parasympathetic reaction such as passivity and thoughtfulness/vigilance to watch out for future dangers very cautious or avoidant behaviors. Here is another example to try and differentiate fear vs anxiety. You are going camping and you think about how there will be spiders & bugs anywhere (anticipatory anxiety). As soon as you get there, you start to pitch your tent. When the spider scurries across your backpack, it sends that stress/fear response into motion. Your body immediately begins to feel endangered—pupils dilate, heart rate increases (notes from the article "True Pain Tolerance: How to Measure Your Mind" 10). Some people can ride the wave to the shore and then just have water lapping at their ankles, for others even when you take away what is triggering this physiological response, getting parts of our brains back out of "fight or flight" doesn't shut off easily. Ultimately, both anxiety and fear responses converge through the same brain pathways, resulting in behavioural and physiological symptoms. They both can also affect how well a person is able to perform everyday tasks.

Context of Anxiety

Now that you have at least an abstract of what anxiety actually IS, with regard to prevalence rates (how common it is) let us put things into perspective further. In fact, anxiety can take many forms and plenty of the numbers below refer to it as a catch-all category. Anxiety and Depression Association of America (2018) stated that, Anxiety disorders are the most common mental illness in the U.S., affecting 40 million adults in the United States age 18 and older, or 18.1% of population every year. Each year, about 7% of children ages 3-17 have problems with anxiety. The vast majority of people who have the condition experience symptoms before they turn 21.While anxiety disorders are highly treatable, only 36.9% of individuals with the conditions actually receive treatment. Individuals with generalized anxiety disorder visit the doctor at three to five times—and

undergo diagnostic tests two times as frequently and X-ray exams seven time more often than those not affected.

table 1 | current treatments for anxiety disorders.

Medication class	Mechanism of action	FDA approvals for anxiety disorder	Off-label uses	Therapeutic dose ranges (mg/day)
SSRIs:				
Fluoxetine	Selective 5-HT	PD	GAD, SAD	20–60
Sertraline	reuptake	PD, SAD	GAD GAD,	50–200
Citalopram	inhibitor (20)	None	PD, SAD PD,	20–40
Escitalopram			SAD	
SNRIs:				
Duloxetine	5-HT, NE (and	GAD	PD, SAD	30–60
Venlafaxine (XR)	DA) reuptake	GAD	PD, SAD	75–300
Desvenlafaxine	inhibitor (17)	None	GAD, PD, SAD	50–100
TCAs:				
Clomipramine	NE and 5-HT	None	GAD, PD,	100–250
Imipramine	reuptake	None	SAD GAD,	100–300
Desipramine	inhibitor (20)	None	PD, SAD	100–200
Nortriptyline		None	GAD, PD, SAD GAD, PD, SAD	50–150
MAOIs:				
Phenelzine	MAO inhibitor (21)	None	GAD, PD, SAD	30–90
Mixedantidepressants:				
Mirtazapine	5-HT2, 5-HT3, α2, H1	None	Anxiety, GAD, PD, SAD	15–45

	antagonist (27)			
GABAergic drugs:				
Pregabalin	Unclear, may	None	GAD, SAD	150–600
Gabapentin	modulate Ca	None	GAD, SAD,	600–2,400
	channels (51)		PD	
Benzodiazepines:				
Clonazepam	GABA-A	PD	Anxiety, GAD,	1–2
Alprazolam	agonist (44)	Anxiety, PD	PD, SAD	1–4
Lorazepam		Anxiety	GAD, PD,	2–6
Chlordiazepoxide		Anxiety	SAD GAD,	20–100
Oxazepam		Anxiety	PD, SAD	30–60
			GAD, PD,	
			SAD GAD,	
			PD, SAD	
Antipsychotics:				
Trifluoperazine	D2 antagonist	Anxiety	GAD, PD,	2–6
Olanzapine	(84) D2, 5-HT2	None	SAD Anxiety,	5–15
Quetiapine	H1 antagonist	None	GAD Anxiety,	50–300
	(85) D2, 5-HT2		GAD	
	H1 antagonist			
	(85)			
Beta-blockers:				
Propranolol	β-1, β-2	None	Anxiety, PD,	60–120
	antagonist (77)		SAD	
Antihistamines:				
Hydroxyzin	H1 antagonist	Anxiety	GAD, PD,	25–100
	(76		SAD	
Other anxiolytics:				
Buspirone	5-HT1A partial	Anxiety	GAD	15–60
	agonist (22)			

Keyword: Serotonin (5-HT); Agoraphobia (AGP); Dopamine (DA); Dopamine-2 receptor (D2); Extended Release (ER); Food and Drug Administration (FDA); Generalized Anxiety Disorder (GAD); Gamma Aminobutyric Acid (GABA); Histamine 1 receptor (H1); Monoamine Oxidase (MAO) and Monoamine Oxidase Inhibitors (MAOI); Norepinephrine (NE); Panic Disorder (PD); Selective Serotonin Reuptake Inhibitor (SNRI); Serotonin Norepinephrine Reuptake Inhibitor (SNRI); Social Anxiety Disorder (SAD); Tricyclic

Antidepressants (TCA). (Medicine for Anxiety Disorders: Up-to-Date and Future Treatment Options) https://frontiersin.org

Busprirone:

❖ Buspirone is fascinating when you think about treating anxiety. This is because, as a 5-HT1A partial agonist, its mode of action differs from many other anxiolytics such as benzodiazepines. More than this, let me break down the key points:

❖ Use and Efficacy:

FDA Approved and Primary Indication: The FDA has approved buspirone as a treatment for GAD, or generalized anxiety disorder. Trazodone is frequently prescribed to patients as an alternate supplement to SSRIs or SNRIs.
Minimally effective: Generalized anxiety disorder (GAD) can be treated with buspirone thanks to FDA approval. Trazadone is frequently recommended to patients as an additional SSRI or SNRI.
It is more effective than placebo, but not as good as those other classes of medications. The evidence comparing buspirone with placebo (no benzodiazepines) was low quality and not useful in terms of findings for people identified as having panic disorder (PD).

Side-Effects & Tolerability :

Frequent Effects: The most common side-effects associated with Buspirone may cause side effects such as nausea, dizziness, and headaches. Less commonly, it has been associated with movement disorders..

❖ **Tolerance**: It is usually less tolerated than other treatments and its effectiveness can be reduced in people who are benzodiazepine-tolerant.

❖ Dosage and Onset:

❖ **Dose**: Buspirone is usually started at two or three times per day.

❖ Open-Accredit: Onset is slow; effects are usually seen over the duration is 10 days to 4 weeks.

❖ **Additional Uses**:

Reduced Libido: Evidence is limited, but buspirone may be helpful in reducing the sexual side effects that accompany SSRI's.

❖ Overall, despite a unique option in the armamentarium for anxiety treatment with buspirone (with potential utility especially among individuals who cannot tolerate other treatments), it frequently is considered a second-line or even lower agent behind SSRIs and SNRIs and benzodiazepines.

Receptor Activity

- Presynaptic: Alpha-2 adrenergic receptor antagonist, which can promote the release of norepinephrine and serotonin.
- Postsynaptic: Antagonizes 5-HT2 and 5-HT3 receptors, the latter possibly mediating its actions as an antidepressant [80].
- Histamine-1 (H1) Receptors: Competes with histaminergic stimulation resulting in sedation and increased weight due to antagonism.

Benefits:

- Encourages growth hormone release – Helps with sleep and appetite
- Safe for use with elderly patients. Less potential for drug-drug interactions.
- Less sexual side effects SSRIs and SNRIs are more effective than other types of antidepressants.
- It is important to note that SSRIs and SNRIs have a higher efficacy compared to other classes of antidepressants.
- **Adverse effect**:
- Weight gain.
- Sedation.
- Dry mouth.

Anxiolytic effects-Anxiety disorders

- **Panic Disorder (PD)**: One small RCT found mirtazapine equally efficacious as escitalopram.
- **Disorder of Social Anxiety (SAD)**: 1 RCT found improved compared to placebo but another study did not demonstrate separation from placebo
- **GAD, or generalized anxiety disorder**: No controlled studies to date.

Mirtazapine

Summary: Mirtazapine can be more robust or should always prove helpful whereas treating nervousness however is primarily an antidepressant. KG: It might be an adjuvant (secondary therapy for anxiety-related conditions.

- **Pharmacological Profile:**
- Dopamine-Norepinephrine Reuptake Inhibitor (DNRI): Blocks reabsorption of dopamine, and nor epinephrine into presynaptic neuron.

FDA Approval: FDA Approved for smoking cessation, attention deficit/hyperactivity disorder (ADHD), and major depressive disorder (MDD).

- Benefits: Might counteract SSRI side effects related to sex

Adverse Effects: As a result, popular belief may actually be accurate in one respect — it does seem to make anxiety worse (although whether that is true or not remains an open question).

- **Efficacy in Anxiety Disorders**
- Anxiety Disorder (GAD): Randomized controlled trial contrasting escitalopram and bupropion XL
- found about equivalent effectiveness.
- Panic Disorder (PD): Data is mixed in terms of efficacy.

Conclusion: Bupropion is not the typical first line for anxiety disorders but has multiple lines of evidence

- behind it suggesting that bupropion might be effective, especially when used in combination with other treatments. Its functions require further investigation.

Nefazodone

Pharmacological Profile: Serotoninergic Modulation: It is a serotonin reuptake inhibitor which makes it inhibit the postsynaptic 5-HT2 receptors.

Benefits:

Some evidence of potential benefits in anxiety disorders

- **Adverse Effects:** Rare but serious liver toxicity has constrained it use

Anxiety Disorders Efficacy of CBD: Parkinson's disease (PD) and Generalized Anxiety Disorder (GAD)- Several open label studies has suggested improvement, however There have not been any controlled studies performed in PD or GAD.

- Social Anxiety Disorder (SAD): There is a non-placebo controlled RCT showing no significant efficacy.

Bottom line: Nefazodone is very rarely used in anxiety disorders because of its rare hepatotoxicity and minimal supportive studies. It was a prospect, but one that is rarely used.

- **Summary**

Mirtazapine: An antidepressant, there is some supporting evidence suggesting mirtazapine may be useful as an adjunctive treatment in anxiety. A major drawback is the potential for weight gain and sedation; improvements in sleep and appetite are advantages.

- **Bupropion** : commonly used for depression and to help quit smoking. Its use in anxiety is less frequent and more tentative but it may also be effective for this application, particularly when used with other treatments.
- **Nefazodon**: Limited by liver toxicity and lack of controlled trial evidence for anxiety disorders Its Current Evidence of Use in Anxiety. Each drug carries a unique signature and can be selected depending on patient-specific desires, expected rewards, and tolerability.

NOVEL TREATMENTS FOR ANXIETY DISORDERS

table | novel medication treatments for anxiety disorders.

Medication Class	Mechanism of action	FDA approvals	Past RCTs in anxiety	Ongoing/future trials in anxiety
Serotonergic agents: Vilazodone	Selective 5-HT reuptake inhibitor, 5-HT1A partial agonist (90)	MDD	GAD (90, 91) SAD (93) Sep. Anxiety (92)	SAD (NCT01712321)
Vortioxetine	Selective 5-HT reuptake inhibitor 5-HT3 antagonist 5-HT1A agonist (95)	MDD	GAD (95–98) PD (99)	Co morbid SAD, MDD (NCT04220996)
Gepirone ER	5-HT1A partial agonist (102)	None	None	GAD (103)
Tandospirone	5-HT1A partial agonist (104)	None	None	GAD
Ondansetron	5-HT3 receptor antagonist (110)	Nausea/vomiting	GAD (110) PD (111)	None
Neuropeptides: Oxytocin	Unclear	Labor induction	SP (184) SAD (188)	Anxiety + depression

				(NCT03566069)
Suvorexant	Orexin 1,2 antagonist (216)	Primary Insomnia	PD (NCT02593682)	None
Natural remedies:				
Kava	Unclear, activity on Na, Ca channels or GABA-A receptor (244)	None	GAD (247)	None
Saffron	Unclear, inhibiting 5-HT reuptake in synapses (252)	None	Anxiety symptoms (252)	GAD (NCT02800733)
Lavender	inhibition of voltage-gated Ca channels (249)	None	GAD (248, 249)	Dental anxiety (NCT04285385) Pre-operative anxiety

Keyword: GABA, Gamma Amino butyric Acid; GAD, Generalized Anxiety Disorder; MDD, Major Depressive Disorder; NMDA, n-methyl-d-aspartate; NRI, Norepinephrine Reuptake Inhibitor; NOS, Not Otherwise Specified; PD, Panic Disorder; RCT, Randomized Controlled Trial; SAD, Social Anxiety Disorder; Sep. Anxiety, Separation Anxiety Disorder; SNRI, Serotonin Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor.

Neuropeptides

Small proteins called neuropeptides are also neurotransmitters molecules that act in many brain processes such as pain relief, reinforcement learning circuits of the brain paging reward system and social interaction learning prefrontal social behavior memory. There is also the question of whether more targeted neuropeptides such as oxytoxin, Neuropeptide Y (NPY), substance P, arginine, and vasopressin (heroicins.com).

Some of the most well known that include gastrin, secretine and cholecystokinin (CCK) respectively; governing parties in modulating fear and anxiety. The neuropeptide oxytocin is in charge of connection and pro-social actions. Because oxytocin is poorly absorbed in the digestive tract, intravenous administration is the only way to administer it; intramuscular or IN administration will not be effective. or sublingually, a well-tolerated method without a history of significant side effects [181]. Empirical studies demonstrate positive impacts on emotion regulation (37, 38). Reduced oxytocin has been linked to increased anxiety (183) and decreased Trust-n-Rec (182). The neuropeptide oxytocin is in charge of connection and pro-social actions. Since it is poorly absorbed

in the digestive system, that means, oxytocin has to be administered. The neuropeptide oxytocin is in charge of connection and pro-social actions.. Animal research indicates that oxytocin has anxiolytic properties. Oxytocin effects and Human research support the hypothesis that oxytocin may relieve anxiety acutely. Take a double-blind, placebo-controlled study, for example. Intranasal Oxytocin and Single-Session Exposure-Based Cognitive-Behavior Therapy for Acrophobia..

Frequency of administration and the context in which it is used [183]. Research Oxytocin for anxiety disorders is on primarily focused on SAD (185, 186), and that those days can see increasing.Same in the amygdala: reduced activity to emotional faces and increased anterior cingulated-amygdalar-prefrontal strength (again for angry face viewing)(187) and improvements in pro social actions (188). While there is undoubtedly an abundance of evidence about the usage of oxytocin with antipsychotics for the enhancement of schizophrenia (189), there are several ranges crucially, however, two of these trials (190) cast doubt on the contentious research design and sample size because it is debatable if oxytocin can get across the blood-brain barrier. Systemic levels corresponded to either intranasal or central dosage. Operation (191). This is based on the single study that is currently known to exist.

Intranasal Oxytocin's Effects On Acute Anxiety And Depression During Hospitalization In A Psychiatric Setting (Psychotic Depression) Are Reviewed Here.

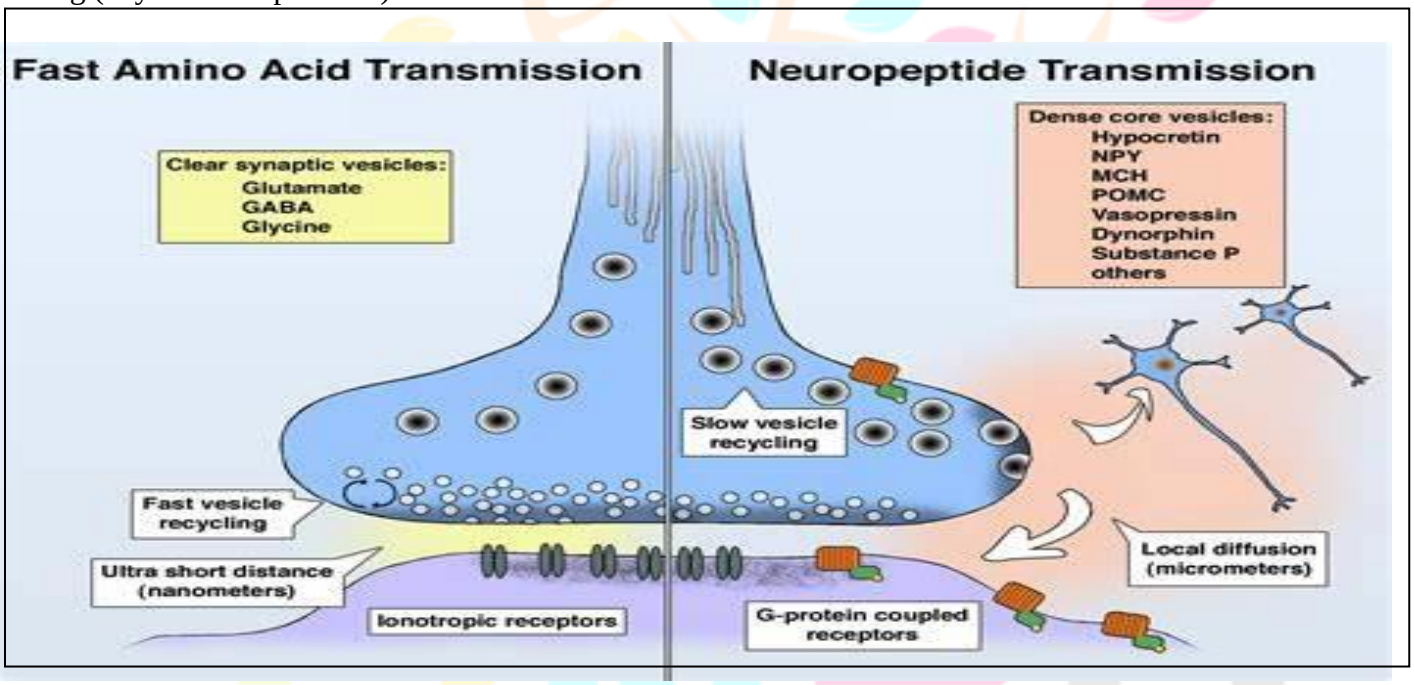

Figure 3: Neuropeptide transmission

SSRIs:

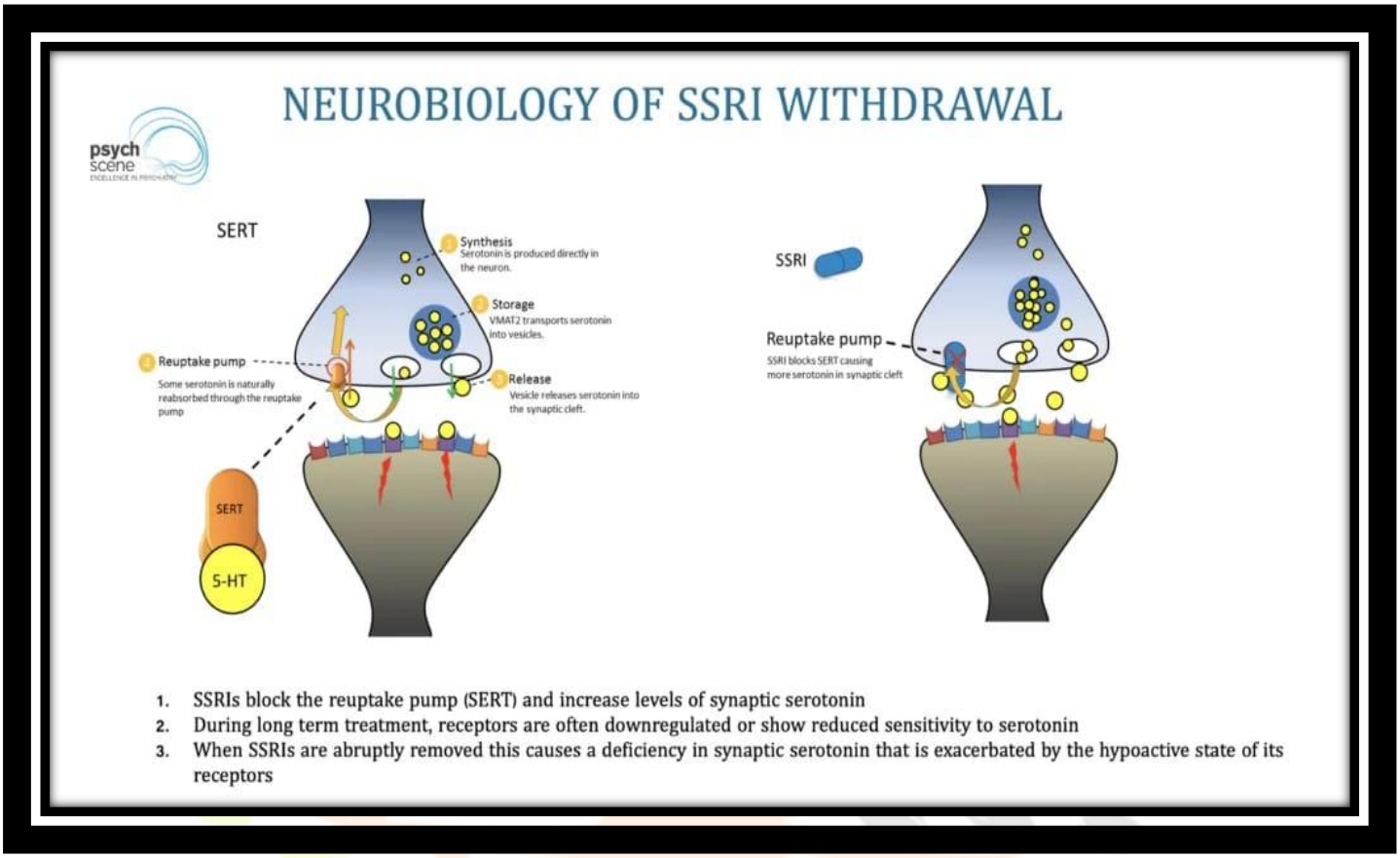

Figure 4: SSRIs

Serotonergic Agents:

There has been extensive research on the connection between anxiety and anxiety disorders and the serotonin system, which is mediated by the brain chemical serotonin (also known as 5-HT). Since serotonin plays a major role in mood regulation, many of the primary anxiety drugs act by interfering with this system. These comprise SNRIs (serotonin-norepinephrine reuptake inhibitors), azapirones such as buspirone, and SSRIs (selective serotonin reuptake inhibitors).

In an effort to replicate the advantages of selective serotonin reuptake inhibitors (SSRIs) but maybe with fewer adverse effects, researchers are now creating novel drugs that target multiple serotonin receptors. Vilazodone is one instance. This medication, which the FDA licensed in 2011 for the treatment of major depressive disorder (MDD), also functions on a particular serotonin receptor (5-HT1A) as a partial agonist. Both social anxiety disorder (SAD) and generalized anxiety disorder (GAD) have been examined with it (). First, a meta-analysis of vilazodone for generalized anxiety disorder (GAD) found that when vilazodone was administered as opposed to when it was assisted by a placebo, "three separate 10-week trials showed greater efficacy." . A more recent meta-analysis raised concerns about the effectiveness of vilazodone for GAD, suggesting that the medication's claims of effectiveness may be exaggerated.

Novel Drug Target:

1) **Neurosteroid Modulators**:

Target: GABA-A receptors.

2) **Glutamate Receptors**:

Target: NMDA and AMPA Receptors.

3) **CRF (Corticotropin-Releasing Factor) Receptors:**

Target: CRF1 and CRF2 Receptors.

4) **Endocannabinoid System**:

Target: CB1 Receptors.

5) **Neuropeptide Y (NPY) System**:

Target: NPY Receptors.

6) **Oxytocin System**:

Target: Oxytocin Receptors.

7) **Glycine Receptors:**

Target: GlyR.

8) **Histone Deacetylases (HDACs)**:

Target: Specific HDAC Enzymes.

Conclusion:

The field of treating anxiety and anxiety-related illnesses is in a critical state, which calls for the creation of innovative pharmacological approaches. The efficacy and patient adherence of traditional therapy are sometimes impeded by their inherent limitations. A viable strategy to address these issues is the investigation of novel targets, such as the glutamatergic pathways, the endocannabinoid system, the GABAergic system, and neuropeptide like oxytocin and vasopressin. Furthermore, our understanding of the pathphysiology of anxiety has advanced significantly due to the therapeutic potential of psychedelics and our growing understanding of neuroinflammation.

Personalized medication development should be given top priority in the future, utilizing biomarker discovery to customize therapies to meet the needs of specific patients. By concentrating on these novel targets, we can create treatments that have a quicker onset of action, improve efficacy, and minimize side effects. In the end, a more sophisticated comprehension of anxiety disorders will result in better treatment outcomes, meeting the pressing demand for efficient and easily accessible solutions for individuals afflicted by these crippling illnesses.

Acknowledgement:

The advancement of therapy options for anxiety and anxiety-related diseases depends on the recognition of novel pharmacological targets in drug development. Several intriguing paths have been research: Neurotransmitter Systems: GABAergic and glutamatergic systems have attracted attention recently, providing hope for novel therapeutic approaches. These systems go beyond conventional targets like serotonin and norepinephrine.

Neuroinflammation: Since anxiety is associated with chronic inflammation, targeting inflammatory pathways has shown potential. Innovative treatments could result from modifying immune responses. Endocannabinoid System: The modulation of anxiety has been linked to cannabinoid receptors. Novel treatment possibilities could be offered by medications that improve endocannabinoid signaling.

Stress Response Pathways: Medication that reduces anxiety symptoms can be developed by taking into account the hypothalamic-pituitary-adrenal (HPA) axis and its function in stress responses. Understanding Genetic and Epigenetic Variations and Epigenetic Shifts

References:

1) Muris P, Rapee R, Meesters C, and Schouten E, Geers M. Threat perception abnormalities in children: the role of anxiety disorders symptoms, chronic anxiety, and state anxiety. Journal of anxiety disorders. 2003 Jan 1; 17(3):271-87.

2) Crocq MA. A history of anxiety: from Hippocrates to DSM. Dialogues in clinical neuroscience. 2015 Sep 30; 17(3):319-25.

3) Nahar LK, Murphy KG, Paterson S. Misuse and mortality related to gabapentin and pregabalin are being under-estimated: a two-year post-mortem population study. Journal of analytical toxicology. 2019 Sep;43(7):564-70.

4) Bailey JE, Papadopoulos A, Lingford-Hughes A, Nutt DJ. D-Cycloserine and performance under different states of anxiety in healthy volunteers. Psychopharmacology. 2007 Sep; 193:579-85.

5) Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. Journal of clinical psychopharmacology. 2007 Jun 1; 27(3):263-72.

6) Van Ameringen M, Mancini C, Patterson B, Truong C. Antiepileptic drugs in the treatment of anxiety disorders: role in therapy. Antiepileptic Drugs to Treat Psychiatric Disorders. 2008 Jun 13:220-63.

7) Griebel G, Holmes A. 50 years of hurdles and hope in anxiolytic drug discovery. Nature reviews Drug discovery. 2013 Sep; 12(9):667-87.

8) Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, Ionescu DF, Mathew SJ, Chang LC, Iosifescu DV, Murrough J. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Molecular psychiatry. 2020 Jul 1;25(7):1592-603.

9) Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, Owoeye O, Batten LA, Blier P. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. American Journal of Psychiatry. 2019 May 1; 176(5):401-9.

10) Mathew SJ, Amiel JM, Coplan JD, Fitterling HA, Sackeim HA, Gorman JM. Open-label trial of riluzole in generalized anxiety disorder. American Journal of Psychiatry. 2005 Dec 1; 162(12):2379-81..

11) Davidson JR. Pharmacotherapy of social anxiety disorder: what does the evidence tell us?. Journal of Clinical Psychiatry. 2006 Jan 1; 67:20.

12) Balon R, Starcevic V. Role of benzodiazepines in anxiety disorders. Anxiety disorders: Rethinking and understanding recent discoveries. 2020:367-88.

13) Bystritsky A. Treatment-resistant anxiety disorders. Molecular psychiatry. 2006 Sep; 11(9):805-14.

14) Torres-Bondia F, De Batlle J, Galván L, Buti M, Barbé F, Piñol-Ripoll G. Trends in the consumption rates of benzodiazepines and benzodiazepine-related drugs in the health region of Lleida from 2002 to 2015. BMC Public Health. 2020 Dec;20:1-9..

15) Rissardo JP, Caprara AL. Buspirone-associated movement disorder: a literature review. Prague medical report. 2020 Mar 19; 121(1):5-24..

16) Hoehn-Saric R, Merchant AF, Keyser ML. Effects of clonidine on anxiety disorders. Archives of General Psychiatry. 1981 Nov 1; 38(11):1278-82.

17) Hoehn-Saric R, Merchant AF, Keyser ML. Effects of clonidine on anxiety disorders. Archives of General Psychiatry. 1981 Nov 1;38(11):1278-82.

18) Pecknold JC, Luthe L, Scott-Fleury MH, Jenkins S. Gepirone and the treatment of panic disorder: an open study. Journal of clinical psychopharmacology. 1993 Apr 1;13(2):145-8.

19) Bansal Y, Bhandari R, Kaur S, Kaur J, Singh R, Kuhad A. Gepirone hydrochloride: a novel antidepressant with 5-HT1A agonistic properties. Drugs of Today (Barcelona, Spain: 1998). 2019 Jul 1; 55(7):423-37.

20) Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, Eisenmenger K, Shiekh M, Otto MW. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. Archives of general psychiatry. 2006 Mar 1; 63(3):298-304.

21) Smits JA, Pollack MH, Rosenfield D, Otto MW, Dowd S, Carpenter J, Dutcher CD, Lewis EM, Witcraft SM, Papini S, Curtiss J. Dose timing of D-cycloserine to augment exposure therapy for social anxiety disorder: a randomized clinical trial. JAMA network open. 2020 Jun 1; 3(6):e206777-.

22) Gordon D, Heimberg RG, Tellez M, Ismail AI. A critical review of approaches to the treatment of dental anxiety in adults. Journal of anxiety disorders. 2013 May 1;27(4):365-78

23) A tack JR. Preclinical and clinical pharmacology of the GABAA receptor α5 subtype-selective inverse agonist α5IA. Pharmacology & therapeutics. 2010 Jan 1; 125(1):11-26.

24) Iftikhar K, Siddiq A, Baig SG, Zehra S. Substance P: A neuropeptide involved in the psychopathology of anxiety disorders. Neuropeptides. 2020 Feb 1;79:101993.

25) Griebel G, Beeské S, Stahl SM. The vasopressin V1b receptor antagonist SSR149415 in the treatment of major depressive and generalized anxiety disorders: results from 4 randomized, double-blind, placebo-controlled studies. The Journal of clinical psychiatry. 2012 Oct 16; 73(11):22142.

26) Zwanzger P, Domschke K, Bradwejn J. Neuronal network of panic disorder: the role of the neuropeptide cholecystokinin. Depress Anxiety. (2012) 29:762– 74. doi: 10.1002/da.21919.

27) Eser D, Baghai TC, Schule C, Nothdurfter C, Rupprecht R. Neuroactive steroids as endogenous modulators of anxiety. Current pharmaceutical design. 2008 Nov 1; 14(33):3525-33.

28) Longone P, di Michele F, D'Agati E, Romeo E, Pasini A, Rupprecht R. Neurosteroids as neuromodulators in the treatment of anxiety disorders. Frontiers in endocrinology. 2011 Oct 19; 2:55.

29) Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, Farrell M, Degenhardt L. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. The Lancet Psychiatry. 2019 Dec 1;6(12):995-1010.

30) Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics. 2015 Oct 1;12(4):825-36.

31) Bergamaschi MM, Queiroz RH, Chagas MH, De Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martín-Santos R. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuro-psychopharmacology. 2011 May; 36(6):1219-26.

32) Bergamaschi MM, Queiroz RH, Chagas MH, De Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology. 2011 May; 36(6):1219-26.

33) Fabre LF, McLendon DA. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. J Clin Pharmacol. 1981 Aug 9;21(S1):377S-82S

34) Ilaria RL, Thornby JI, Fann WE. Nabilone, a cannabinol derivative, in the treatment of anxiety neurosis. Curr Ther Res Clin Exp. 1981; 29:943-9.

35) Singh YN, Singh NN. Therapeutic potential of kava in the treatment of anxiety disorders. CNS Drugs. 2002; 16:731-43. doi: 10 .2165/00023210-200216110-00002.

36) Pittler MH, Ernst E, Cochrane Common Mental Disorders Group. Kava extract versus placebo for treating anxiety. Cochrane Database Syst Rev. 2010;(6)

37) Smith K, Leiras C. The effectiveness and safety of Kava Kava for treating anxiety symptoms: A systematic review on clinical trials. Complement Ther Clin Pract. 2018 Nov;33:107-17

38) Ooi SL, Henderson P, Pak SC. Kava for generalized anxiety disorder: a review of current evidence. J Altern Complement Med. 2018; 24:770-80. doi:10.1089/acm.2018.0001.

39) Marx W, Lane M, Rocks T, Ruusunen A, Loughman A, Lopresti A, et al. Effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. Nutr Rev. 2019 Aug; 77(8):557-71.

40) Masdrakis VG, Papadimitriou GN, Oulis P. Lamotrigine administration in panic disorder with agoraphobia. Clin Neuropharmacol. 2010 May; 33(3):126-8.

41) Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014 Jul;14:1-83.

42) American Psychiatric Association. Practice guideline for the treatment of patients with panic disorder. Washington, DC; 2009 (42).

43) Sartori SB, Singewald N. Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders. Pharmacol Ther. 2019 Dec; 204:107402.

44) He H, Xiang Y, Gao F, Bai L, Fan Y, Lyu J, et al. Comparative efficacy and acceptability of first-line drugs for the acute treatment of generalized anxiety disorder in adults: a network meta-analysis. J Psychiatr Res. 2019 Nov;118:21-30

45) Bakker A, Van Balkom AJ, Spinhoven P. SSRIs vs. TCAs in the treatment of panic disorder: a Meta-analysis. Act a Psychiatr Scand. 2002 Sep;106(3):163-7

46) Steenen SA, Van Wijk AJ, Van Der Heijden GJ, van Westrhenen R, de Lange J, de Jongh A. Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. J Psychopha20rmacol. 2016 Feb;30(2):128-39