

# GABA System in Anxiety Disorders: A Review of Current and Novel GABAergic Drugs

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**Abstract.** This is an article for defying diverse of drugs in GABA system showing effect in treating anxiety or not. In the passage, the authors discuss the effect and side effect of levetiracetam, gabapentin and pregabalin, tiagabine, and several novel medications which are AZD7325, PF-06372865, BNC-210, SAGE-217. Some of these drugs were certified and has been put into use for decades, while others may be lack of solid test or further experiment for treating anxiety disorders. The main aim of review is evaluating the recent evidence to find out the included GABAergic drugs' potential that is most likely to be beneficial for future therapy of treating anxiety disorders, listing the effect and side effect according to the research, and making comparison to other types of anti-anxieties. In the result, BNC-210 and SAGE-217, as the novel GABAergic drug, are more effective than others, also with less and mild side effects. All the evidence are collected from the papers that written by authorities.

**Keywords:** Anxiety, GABAergic drug, side effect.

## 1. Introduction

The most prevalent mood illness is anxiety disorders., increasing significant financial burden on national public health system. Among U.S. population, 6.8 million adults suffer from generalized anxiety disorder (GAD) [1]. For other types of anxiety disorders, the statistics also show 6 million adults with panic disorder and 15 million adults with social anxiety disorder. Longer time experience for symptoms of anxiety disorder before seeking help is found in this group of people. According to DSM-5, there are differences between each subunit in the group of anxiety disorders [2]. After the consideration through neurobiological and phenomenological bases, both posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) were excluded from the group of anxiety disorders. The separation is also for Agoraphobia, which now has been a single diagnostic class. Because anxiety disorders' categorization has recently undergone alterations, this review will emphasize two prevalent disorder which are GAD and SAD, and the stress, fear from mood perspectives.

The treatment for anxiety disorders has been developed in both psychotherapeutic aspects, like cognitive behavioral therapy or exposure therapy, and pharmacological aspects. Although there is an increasing trend for prevalence of anxiety disorders among college students, seeking help behavior have a significant rise [3]. This may because of the improvement of medication and propaganda of therapy services. The precise use of the drug and the mechanism of the drug itself determine the efficacy of the treatment. For example, through a long history, Benzodiazepines have been used in medication treating anxiety disorders, and are deemed as the most prevalent psychiatric prescription in the world. It is a GABA-A agonist and is highly versatile that can be used not only for anxiety disorders, but also for a variety of conditions. The short-term effect of Benzodiazepines can treat symptoms of anxiety disorders more rapidly, and it is most used in conjunction with SNRIs and SSRIs [4]. However, the side effects of Benzodiazepines, in term of drowsiness, dependence, confusion, muscle weakness, memory problems and dizziness, have troubled today's scientific fields for many years since it has been developed. The reason that Benzodiazepines remain such wide influence is their basic mechanism, acting in GABAergic system.

In this review, we are going to summarize the recent findings of both current GABAergic drugs and novel GABAergic drugs and do comparison and evaluation from the evidence we found. Unlike current GABAergic drugs, novel GABAergic drugs have relatively less evidence based, but it does not mean that novel GABAergic drugs are less effective than current GABAergic drugs or Benzodiazepines for treatment of anxiety disorders. Recent evidence has put some optimistic perspectives for novel GABAergic drugs, precisely suggesting that the potential of them may avoid the existing adverse events. Future studies and public health system may take advantages of that to make improvement for medication with good effectiveness and less side effects. Our review will make clear to both mechanism and effectiveness of current GABAergic drugs and novel GABAergic drugs. Also, the potential of comparing through the stage of other types of anti-anxieties, possible weaknesses and the field future targeting will be revealed.

## **2. Relation between GABA and anxiety disorders**

Many brain regions are responsible for regulation and recognition of emotional stimuli. Amygdala which has a role in regulation of negative moods is deemed as an essential region to explain anxiety disorders. Many studies have detected different regions in brain in response to anxiety of the activation condition and negative emotional stimuli, and the constant finding of these investigations is that amygdala activation. Antidepressants that modulate serotonin neurotransmission have been used as the First-line medication for DSM-5 anxiety disorders, like serotonin noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs). Benzodiazepines although fail to show up in First-line medication, they are also commonly used to treat DSM-5 anxiety disorders, and there are evidence-based studies to suggest their effectiveness as GABA-A receptor positive allosteric modulators, enhancing overall GABA activity. They can rapidly improve the symptoms of anxiety, unlike serotonin type antidepressants take longer to produce the effect, which may be because their modulation to the GABA system.

In animal models, GABA receptor agonists or GABA were injected into the amygdala, which decreased levels of anxiety and fear, in contrast to GABA antagonists, which tended to increase anxiety [5]. Numerous investigations on experimental animals have shown that the regulation of anxiety-related behaviors in the amygdala can be affected by GABAergic neurotransmission. Theoretically, the amygdala's exclusively internal GABAergic intercalated neurons can regulate central nucleus (CeA) activation through basolateral amygdala complex (BLA). The physical manifestation of anxiety is caused by the stimulation of these neurons, in which GABAergic neurons play an inhibitory role.

The expression of anxiety involves many different neurotransmitters brain pathways coordinate activities, all of these neurotransmitter's interaction, and by local and distant regulate synaptic relays. Although, for regulation to the anxiety responses in the amygdala, GABA is not the only one neurotransmitter (others like: endocannabinoids, serotonin, opioid peptides and so on) and medication targeting (others like: glutamate modulators, serotonergic agents, or some natural remedies), this neurotransmitter system has been always the core to anxiety treatment and is the target of benzodiazepines and related medications.

## **3. Current GABAergic drugs**

### **3.1. Levetiracetam**

Levetiracetam (LEV) is an antiepileptic drug, which its mechanism has been well understood. While it is used widely in treatment of Epilepsy, some reports suggest its potential of treating anxiety due to its possible multitargeting. Indirect modulation by LEV to the GABA system increases the concentration of GABA. Studies in early years for detecting the effectiveness of LEV in treatment of social anxiety disorder are limited. There is some evidence to show the tolerance and effectiveness of LEV, but LEV failed in treatment of severe social anxiety patients [6]. For general anxiety disorder,

when the level of anxiety was assessed through Hamilton Anxiety Rating Scale and Zung self-rating Scale for Anxiety, the treatment of LEV illustrates substantial reduction in anxiety [7]. In recent years, the effect of different doses of LEV have been assessed through the animal model. Both low dose group and high dose group exhibited reduced anxiety-like behavior., and prenatal exposure to LEV may result in less anxiety-behavior in adolescence [8].

Some animal studies report skeletal changings result from prenatal exposure to LEV, while visible skeletal changing is absence in the study [8]. Potential side effects should be discovered. In another animal study, Wistar rats were divided into two groups, one receiving repeated doses and the other receiving a single dose. Repeated intaking of LEV disturbed rats' locomotor activity and recognition memory, and a single dose affected emotional memory [9]. The study revealed the potential side effects of LEV on memory and locomotor. Indeed, modulating GABA system which is an inhibition system may have the chance on not only working for inhibiting agitation, but also slowing down normal body functioning. Besides the common side effects for LEV, including Drowsiness, dizziness and headache, other weaknesses still need to be confirmed in the future. Existing evidence is limited to generate to a significant result for evaluation of LEV treatment. Scarce sample size lowers the generalizability of the finding [7]. Although the effect of LEV on treating seizure has been well-established, for anxiety disorders, it needs more solid evidence.

### 3.2. Gabapentin and Pregabalin

Similarly, pregabalin and gabapentin are FDA-approved for treating partial seizure. They also are used in treatment of post-herpetic neuralgia, neuropathic pain, and anxiety disorders. In the scientific field, gabapentin and pregabalin are deemed as analogues to mimic the effects of GABA, instead of binding to GABA receptors, binding to 2-calcium voltage-gated channels in the central nervous system.

In a meta-analysis, gabapentin and pregabalin were assessed on treatment of anxiety insomnia and bipolar disorder. 55 double-blind randomized controlled trials suggest that gabapentin and pregabalin have the effect on reducing preoperative anxiety, with only moderate evidence supported [10]. Because of the research population's diversity, outcome measures and design, no quantitative synthesis could be performed [10]. In the whole spectrum of anxiety, compared with placebo, gabapentin drugs with a consistent but it is not a universal appeal [10]. Theoretically, Pregabalin has more effectiveness as a 2- ligand and is more rapidly absorbed and accessible over the whole dosing range. In another meta-analysis singly assessing pregabalin, 8 studies demonstrate that symptoms of patients with general anxiety disorder significantly decrease [11]. The dropout rates of Pregabalin group were lower than that of benzodiazepine group [11]. Through the comparison, while pregabalin and benzodiazepine both have the effect on improvement of treating anxiety, pregabalin have fewer side effects and no withdrawal syndrome happened.

Potential side effects of addiction and drugs dependence may be found in patients using gabapentin and pregabalin. A systematic review, including 106 studies, detects the addictive power of gabapentin and pregabalin. However, like the reports mentioned above, gabapentin and pregabalin have less addictive power than benzodiazepine. Included reports show the limited reward properties, and less drug dependence cases were found [12]. The gabapentin and pregabalin dependence can be found in those who have experience to addiction and drugs dependence, but the number of them are still less [12]. Comparatively, pregabalin users have more chance to involve in dependence problems, which may be due to the greater potency of pregabalin. Risk factors of gabapentin and pregabalin are obvious and noticeable during the combination of medication. For example, the mixture of opioids and sedatives (gabapentin and pregabalin) may result in harmful effects, even death [12].

### 3.3. Tiagabine

Tiagabine is an antiepileptic drug which has been approved before 2000. It blocks reuptake of GABA to increase the concentration of GABA. An early study implies a double-blind, crossover, randomized design, including eight adults and lasting 4 to 5 months. Eight individuals with social

anxiety disorder were divided into the gabapentin or tiagabine groups randomly. Both gabapentin and tiagabine have the effectiveness to treat social anxiety disorder, also demonstrate the potential that having less side effects than SSRIs and benzodiazepine [13]. Although, the subject size in study mentioned above is needed to be enlarged, many early data appear to indicate the effectiveness of tiagabine in the treatment of anxiety disorders. A large sample size study including 266 patients with GAD, was designed to a randomized placebo-control trial. After 8 weeks, the patients who experienced tiagabine treatment had a significant improvement on Hamilton Anxiety Scale scores [14].

Concern about effectiveness of tiagabine is less likely to be found, with only few studies to question this. However, in recent year, a meta-analysis has compared the common drugs for general anxiety disorder. 30 studies were included, with Hamilton Anxiety Scale-based, double-blind, randomized, controlled studies for determining remission. For remission, tiagabine is less effective than other common drugs, including agomelatine, duloxetine, escitalopram, quetiapine, and venlafaxine [15]. For tolerability, tiagabine also perform worse than both other drugs and placebo, resulting in common side effects like dizziness and headache [15]. Tiagabine can be used to treat many diseases, not only for anxiety, also for certain types of seizures. The existing findings suggest that for treatment of anxiety, tiagabine may not be a priority.

#### 4. Novel GABAergic drugs

Given the effectiveness of benzodiazepines (GABA-A agonists) in treating anxiety disorders, and the potential benefits of existing common anti-anxieties, new GABAergic anti-anxieties have been sought after. Recent papers have suggested four compounds: AZD7325, PF-06372865, BNC-210 and SAGE-217.

##### 4.1. AZD7325

AZD7325 is a selective modulator and high affinity modulator of the GABAA receptor system, with high binding affinity at GABAA $\alpha$ 1,  $\alpha$ 2 and  $\alpha$ 3, and low binding affinity at GABAA $\alpha$ 5. Some evidence show that it has the potential to treat anxiety disorders. Four weeks randomized controlled trial demonstrates the anxiolytic effect of AZD7325 in treatment of general anxiety disorder [16]. A recent review also supports this potential of AZD7325, and the detectable side effects were less than benzodiazepines or possibly than other anti-anxiety drugs [17].

Developing selective ligands for the GABAA receptor subunit may lead to the emergence of novel effective anti-anxiety drugs that avoid the sedative effects and dependence which benzodiazepines have. However, several studies questioned the effectiveness of AZD7325. The difference between AZD7325 group and placebo group is not significant and have poor tolerability [18]. Through the consideration to pharmacokinetics and sub-optimal adherence in patients, the future development and assessment are still needed.

##### 4.2. PF-06372865

Through the design, evaluation, and optimization of a novel GABAA ligand-gated ion channel subtype selective positive allosteric regulator (pam) based on imidazolpyrazine, the potential of PF-06372865 has been suggested [19]. A study investigated its analgesic potential include both PF-06372865 and pregabalin. 20 participants taking either 15 or 65 mg of PF-06372865 were assigned to pain tasks including pressure, electrical stimuli, cold or heat stimuli, inflammatory pain and the paradigm of conditioned pain modulation. An increasing tolerance threshold for pressure pain have been found in 15mg PF-06372865 group [20]. Pregabalin also increases tolerance threshold, and there is no significant sedation or adverse effects in PF-06372865 group, revealing its effect on release pain and pressure [20]. Common adverse effects of GABAergic drugs can be the comparison. Somnolence, dizziness, bluntness may be less likely to happen in PF-06372865 intaking. 16 healthy adult subjects were divided into two groups according to the difference in dose of PF-06372865. Serial

pharmacokinetics samples were recorded through the days 1 to 21. While the dizziness is the main adverse effect, others are mild, and no somnolence can be found [21]. The findings suggest that PF-06372865 is safe, well tolerated and have the absence of withdrawal symptoms [21].

The effectiveness of PF-06372865 in treatment of anxiety disorders is a question. Many studies have assessed the potential of PF-06372865 in various degree, but few evidence can be found in anxiety field. Due to some business reasons, Phase-2 trial for anxiety was terminated [22]. The existing findings may explain this termination that the efficacy of PF-06372865 is not significant. 90 subjects with general anxiety disorder were randomized into PF-06372856 group and placebo group. 7.5 mg and 2.5 mg of PF-06372856 twice daily were contrasted with a placebo. The evaluation was held through Hamilton Anxiety Inventory and Sheehan Disability Scale. In 7.5 mg PF-06372856 twice daily group, somnolence was relatively more likely to be found [23]. For the efficacy, both PF-06372856 groups failed to separate from placebo group [23]. If the potential of PF-06372865 can be certified, more studies are still needed.

### 4.3. BNC-210

BNC-210 is a nicotinic receptor  $\alpha 7$  negative-allosteric modulator. Preclinical evidence implicates that cholinergic modulation have the effect on regulate the hyperactivity of amygdala and prefrontal cortex. In another theory, BNC-210 may also be the GABA modulator. While the cholinergic modulators have gained less attention in scientific field, several studies suggest the potential of BNC-210 in treatment of anxiety, based on the relationship between emotion and amygdala. The result is optimistic. In a recent report, BNC-210 has been studied with the comparison of placebo and lorazepam. Anxious mood was evaluated through neural responses to fearful stimuli. The injection of BNC-210 to the patients with general anxiety disorder, in the result, reduced the reaction of facing to fearful stimuli and separated from the placebo and lorazepam [24]. Modulating cholinergic neurotransmission can change how neuronal circuits in generalized anxiety disorder work, which suggests that this system can be a novel target for anxiety medication therapy [24].

Due to the mechanism of BNC-210, some adverse events in common anti-anxiety drugs may not be shared. The development of anti-anxiety medications with cholinergic modulating properties may open up new avenues for treating anxiety disorders without the drawbacks of currently available anti-anxiety medications. However, there is a lack of data, evidence and evaluation to the BNC-210. Some of studies reveal that it is a well-tolerated and effective drug to treat anxiety, but the existing suggestion may be: 1. Next stage trials are required for its indication and efficacy; 2. Considering and comparing the competitor compounds; 3. Find the latent side effects [25].

### 4.4. SAGE-217

SAGE-217 is a positive allosteric modulator for GABAA receptor and is also called Zuranolone. In preclinical models, brain slice preparation shows that SAGE-217 can increase the GABA current [26]. Through the oral dosing, SAGE-217 exhibits strong GABAA receptor regulation action in the brain [26]. A recent study suggests that SAGE-217 can be used in the medication of anxiety and depression. Anxiety is further investigated in this study to test the effectiveness of SAGE-217 in improving patients' symptoms of anxiety. The investigation to anxiety outcome includes 151 patients with postpartum depression. From day 15 to day 45, patients in SAGE-217 group have significant reduction in Hamilton Anxiety Rating Scale score [27]. Due to the optimistic result existed, the potential of SAGE-217 has been continuously studied by its effect on anxiety disorders, bipolar depression and treatment of depression.

The side effects of SAGE-217 is significant, including sedation, headache, somnolence, diarrhea, upper respiratory tract infection and dizziness [27]. In the placebo-controlled, double-blind, phase I trial, the tolerated dose and safety was evaluated. 108 healthy subjects were assigned to either single ascending multiple ascending dose group or dose group. This trial reveals that most side effects are mild, dose-dependent, and well-tolerated [28]. In the next double-blind, phase 2 trial which investigates the patients with major depression, showed the improvement in anxiety and depression.

Although there were no severe adverse effects, common events like somnolence, dizziness, headache, and nausea, had been further certified [29]. Unlike other novel drugs which are deferred by various reasons, the side effects of SAGE-217 are less likely to be the later impairment for being approved, but to be the opportunity for well-studied. In the future, SAGE-217 should be studied for more evidence to encourage its efficacy in both depression and anxiety, and for confirming the safely recommended dose, as there are limited resources for now.

## 5. Evaluation

Some side effects for common GABAergic drugs are clear due to their mechanism, but skeletal changings are found in the earlier study of LEV [8]. Based on the evidence above, Tiagabine intake only resulting in relatively less side effects. The addictive power of gabapentin and pregabalin is under suspicion, but it is more relied on the case. Patients without history of substance abuse have possibly no chance to be addicted to gabapentin and pregabalin [12]. By comparing to the benzodiazepines, gabapentin and pregabalin have more mild side effects [11], so does the AZD 7325 [17]. While the mechanism and reaction have not well studied for novel GABAergic drugs, their side effects are generally more gentled. PF-06372865 and SAGE-217 have the common GABAergic drugs' side effects, like headache, sedation and dizziness [20,29]. Because BNC-210 is a mild drug which dose the modulation in a different way, its side effects should be further studied.

The weakest point for common GABAergic drugs is their effectiveness in treatment of anxiety disorders, although they have been studied for so many years. Unlike the LEV, Gabapentin and Pregabalin which the effectiveness is questioned by several reports, Tiagabine as a well-supported drug is still proved to less effective than other types of drugs like SSRIs or benzodiazepines [15]. The common drugs, including LEV, gabapentin, pregabalin and Tiagabine, though they have been studied in many scientific field, existing evidence is not solid for them to have a big achievement in treatment of anxiety disorders under this drug-competitive environment, unless in the case of precise medication recommending (gene test). Less evidence is based for novel GABAergic drugs, including AZD 7325, PF-06372865, BNC-210 and SAGE-217. In terms of them, the potential of AZD 7325 and PF-06372865 is rejected by several studies, saying that the performance of them fail to separate that of placebo [18,21]. They may need more reports to demonstrate the effectiveness, or otherwise they may face to be terminated. On the one hand, the prospect of BNC-210 and SAGE-217 is more optimistic. Both have been proved to have the effective potential of treating anxiety disorders. SAGE-217 currently have been put to the study of treating multiple mood illnesses, such as anxiety disorders, bipolar depression and depression, and its effectiveness are significant and side effects are clearly detected. BNC-210, in recent study, have been proved to diminish the symptoms of genialized anxiety disorder and the fearful mental state [24]. On the other hands, both drugs are lack of the evidence based. Further studies are coming in to examine the effectiveness and potential adverse events of BNC-210 and SAGE-217.

Based on the pharmacological mechanism of the drugs mentioned above, although different side effects can be found among current GABAergic drugs, like the potential possibility of skeletal changings in LEV treatment, the effects of those drugs are clinically shared, and working on many clinical treatments. For example, existing current GABAergic drugs commonly have the effect on seizure, panic disorder and so on. As a result, in the future, the experiment and clinical trial of novel GABAergic drugs may not only test the effectiveness of their treatment on depression and anxiety, but also test for other mood disorders or physical disorders. The existing novel GABAergic drugs, for example, BNC-210 and SAGE-217, are more likely to be further studied and widely tested, according to their performance in recent clinical trials. The effectiveness of AZD7325 and PF-06372865 in the treatment of anxiety disorders may need more solid evidence or may be tested through other clinical fields, despite the existing evidence's failure to support that.

## 6. Conclusion

More studies will come out for solving the current problem according to the performance of GABAergic drugs. Firm termination of certain drug may not be the tendency for future development, which is also not common. Several GABAergic drugs with relatively weak anti-anxiety effect have the role in another clinical field, like seizure. The Side effect is complicated to be certified through the development of GABAergic drugs, for both novel and current. Under the consideration of effectiveness versus side effects, BNC-210 and SAGE-217 are the drug which may lead current GABAergic drugs to an improving direction.

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All the authors contributed equally and their names were listed in alphabetical order.

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