

History Repeats Itself: Pharmacodynamic Trends in the Treatment of Anxiety Disorders

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Abstract: The original treatment indicated for those suffering from neurotic anxiety was to employ psychotherapy to facilitate changes in behavior and coping with stressful events. A spectrum of somatic treatments “from cathartics and emetics to opium and “strengthening tonics”, from atropine and digitalis to potassium bromide and chloral hydrate, from barbiturates to benzodiazepines”, to serotonergics, came to be used as well [1]. The Food and Drug Administration originally approved many gamma-aminobutyric acid (GABA) facilitating drugs since the 1960s for anxiety treatment. The 1980s evidenced the approval of a few serotonergic treatments that cornered the prescribing market and the front line of most treatment protocols. More recently, GABAergic drugs are making a return in the treatment of anxiety disorders. The following paper details the pharmacodynamic history of treating anxiety and also updates the reader as to the newer GABA-based approaches mentioned above.

Key Words: Anxiety, GABA, Serotonin, Medication.

INTRODUCTION

Historically, psychotherapy for the neurotic anxiety disorders (panic, generalized anxiety, social anxiety, phobias) was the first available treatment to provide symptom relief and cure for anxiety. Dynamic psychotherapy was a long term treatment which aimed to develop insight in the patient about his or her underlying psychic conflicts and the goal was to resolve the conflict and cure the anxiety. We have seen advancement in the psychotherapeutic treatment of anxiety disorders with the advent of short term intensive dynamic psychotherapy and cognitive behavioral therapy. The latter is also a short term treatment and it has been studied comparable to modern day medications. Many forms of psychotherapy have now been shown to lower anxiety symptoms.

Anecdotally, the first pharmacologic treatment for anxiety was most likely ethanol in the form of beer, wine or liquor. This may have been prescribed by a physician, or even more commonly used as an over-the-counter medication. As this is a legally available substance, there has never been an FDA approval or indication for alcohol and its only remaining treatment indication in medicine is when it is used intravenously to treat severe alcohol withdrawal in the hospital setting. In theory, alcohol has been noted to be a social lubricant that promotes lower levels of inhibition and social anxiety. Generally anxious patients often drink alcohol to lower rumination in order to fall asleep or alleviate agitation. Panic disorder patients and phobic patients may also drink to lower anxiety and agitation. Finally, post traumatic stress disorder patients often drink to lower anger and irritability and also to promote numbing of traumatic memories. In

effect, many anxiety patients are thought to self-medicate using alcohol.

In regards to research in this area, there are very few studies that have looked at alcohol's effectiveness in treating anxiety disorders. Research has examined the effectiveness of moderate alcohol consumption in reducing panic and anxiety as an explanation for high co-occurrence of anxiety disorders and alcohol use disorders. Kushner *et al.* report on this link between anxiety and alcohol use given the relative comorbidity of these disorders [2] and also discuss a small study where alcohol reduced panic in subjects [3]. Khantzian, furthermore discusses the link between ego defenses, psychopathology and alcoholism as a link [4]. Eddy performed a small study where problem drinkers showed more anxiety reduction with alcohol use than non-drinkers, [5] and Holroyd's small study suggests that socially anxious people actually drink less in social situations and have lower blood alcohol content compared to non-socially anxious people [6]. As is noted, there are no major, statistically powered studies in this area, and many of these smaller studies show conflicting results where ethanol anxiolysis is concerned.

What is the proposed mechanism of alcohol induced anxiolysis? It's mechanism of action revolves around the GABA (gamma Aminobutyric Acid)-A receptor. GABA is the central nervous system's most abundant inhibitory neurotransmitter. The presence of GABA in neural tissue tends to hyperpolarize neurons. This hyperpolarization occurs when GABA neurotransmitter binds to GABA-A receptors on neurons. Negatively charged chloride ions are allowed to flow down chemical gradient and into the neuron's cell body. This electrochemical negativity inhibits the neuron and decreases the likelihood of its firing further electrical impulses. As GABA levels and GABA activity rises, neuronal firing and activity lowers.

Alcohol, as a molecule, attaches to the GABA-A receptor and acts as an allosteric modulator. If an alcohol molecule

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binds to a GABA receptor, in the presence of a GABA molecule, then there is a synergistic effect whereby the GABA receptor is more efficient and more amenable to allowing chloride to enter the neuron. Alcohol therefore allows more chloride influx and more inhibition of neuronal firing than when GABA is alone in the central nervous system. Alcohol facilitates or improves GABA activity at the GABA receptor. Alcohol has a clinical dose-response curve and this provides for a clinical spectrum of initial anxiolysis, social disinhibition, GABA toxicity (slurred speech, ataxia), stupor, coma, and possibly death through respiratory suppression.

This direct modulation, where alcohol binds to the GABA receptor allows for downregulation (lower quantities) of GABA receptors with long term drinking, also seems to cause a structural change in the protein structure of the GABA receptor itself. These two physical changes may explain tolerance to, and dependence on alcohol where a chronic drinker needs more alcohol to achieve the same clinical effect over time.

THE PHARMACODYNAMIC HISTORY OF TREATING ANXIETY DISORDERS

I. The Age of GABA

A. Barbiturates

The first GABA-based medications were the barbiturates. These medications have been used and FDA approved to treat various forms of epilepsy and even anxiety. Barbiturates have a very similar mechanism of action to that of ethanol. They are also allosteric modulators of the GABA-A receptor. They bind to a separate site that is different in location to where alcohol binds, but the net effect is the same. A barbiturate molecule, when attached to the GABA receptor and in the presence of GABA neurotransmitter, will allow for a markedly increased flow of chloride ions into the neuron compared to GABA alone. This results in lower neuronal firing [7].

The seizure model of using a GABA facilitating drug to lower actual neuronal firing to lower seizure activity was then borrowed and applied to anxiety disorders. If excessive neuronal firing caused seizures, then perhaps, excessive firing may cause worry and panic? Initial studies and approval came next in regards to treating anxiety. Studies on barbiturates suggest that using GABA facilitation (similar to that for seizure control) also tends to lower anxiety levels. In the times of the DSM-I and II the anxiety spectrum disorders were not as categorical as we know them now. Therefore these studies addressed the clinical "relief from anxiety" as a generic entity. Uhlenhuth *et al.* compared meprobamate and phenobarbital to placebo in the treatment of anxiety. Results showed reasonable efficacy [8, 9].

The clinical problem associated with the barbiturates is their tendency to promote tolerance, dependence, and withdrawal. They are highly addictive substances. In a recent study, Zawertailo *et al.* compared the abuse liability of barbiturates versus benzodiazepines and found that this is much more significant for butabarbital than for nonbarbiturates, triazolam and meprobamate. In fact, surprisingly,

meprobamate did not separate from placebo on euphoria and abuse potential scales [10].

Roache *et al.* found similar or greater subject ratings of drug liking and monetary street value for meprobamate when compared to lorazepam. In their study lorazepam (a benzodiazepine) was identified as being more likely to produce adverse behavioral effects such as performance impairment [11]. Barbiturates also promote a spectrum effect of anxiolysis through coma. An intentional overdose is often lethal in a suicide attempt. The risk is greater when mixed with alcohol. There is no way to treat an overdose with barbiturates outside of using a ventilator. Oftentimes, respiratory suppression and death occurs. They are also difficult to dose as they have non-linear pharmacokinetics, hepatic autoinduction and metabolism, no clear dose response curve, and extensive half lives. These agents have largely fallen out of practice in treating anxious patients, even if rare studies are still published where tetramate was found to be equivalent to lorazepam in terms of the efficacy of treating generalized anxiety disorder. They showed some advantages in the tetramate group: better global tolerance, lesser frequency and severity of withdrawal symptoms during the treatment taper [12]. Possibly the only remaining clinical use is in alcohol withdrawal and detoxification.

B. Benzodiazepines

The benzodiazepines next entered the clinical scene as both FDA approved anxiolytics, sedative-hypnotics, anesthetics, and antiepileptics. These drugs are also GABA facilitating in a manner exactly similar to both ethanol and the barbiturates. The only difference is that the benzodiazepine molecule has its own separate binding site (as opposed to the ethanol binding site and the barbiturate binding site on the GABA receptor itself). The mechanism of improving chloride influx and neuron hyperpolarization is exactly the same as well.

The benzodiazepines have been used in a large spectrum of anxiety-related conditions. Early studies found effectiveness in "anxiety neurosis", phobic avoidance behavior and phobic anxiety, in treating "anxiety syndrome" in hospitalized patients, or anxiety associated with schizophrenia [13-16].

When considering "generic anxiety", numerous studies found a relative equivalence in terms of efficacy when comparing diazepam with clorazepate, alprazolam, clobazam, or prazepam [17-21]. It is problematic in that these early studies did not often differentiate between specific anxiety disorders, and response rates could widely vary as different anxiety subtypes may be harder, or easier, to treat. In the 80's, more anxiety specific placebo controlled studies found effectiveness of various benzodiazepines in the treatment of panic disorder: first diazepam (with addition of propranolol), then alprazolam, followed in the 90's by clonazepam [22-25].

The minimum effective dose of clonazepam was 1 mg daily, and side effects of somnolence and ataxia were more often present for doses higher than 3-4 mg daily [26]. At 6 weeks of treatment using a fixed dose of 2 mg daily 61.5% of the patients were panic free compared with 11.1% in the placebo group [27]. In a study following 204 patients treated with clonazepam for panic disorder over a 2-year period,

Worthington *et al.* indicated that the short-term therapeutic benefit can be maintained over time without the development of tolerance and dose-escalation [28]. This replicates an older study with similar results [29]. The literature cites use of sodium valproate as augmentation of clonazepam for treatment resistant panic disorder, but often, these days, clonazepam is used in addition to an SSRI for the treatment of panic disorder [30]. Pollack *et al.* found that combined paroxetine and clonazepam treatment resulted in more rapid response than the SSRI alone, but there is no differential benefit beyond the initial few weeks [31]. This finding was replicated with sertraline and clonazepam. At week 3 of treatment 63% of the sertraline/ clonazepam group versus 32% in the sertraline alone group were responders [32]. A gradual taper (up to 7 weeks) of the clonazepam after the initial weeks of treatment seemed to avoid complications with withdrawal symptoms and worsening of anxiety symptoms as suggested by Moroz *et al.* [33].

Another anxiety condition of particular importance for the use of benzodiazepines is generalized anxiety disorder. Fontaine *et al.* found bromazepam to be more effective than diazepam and both to be more effective than placebo in a 4 week treatment of generalized anxiety disorder [34]. Similar efficacy compared to placebo was found for lorazepam [35]. Elie found similar efficacy for diazepam and alprazolam in the treatment of GAD, although diazepam was found to be more efficient than alprazolam in the reduction of several symptoms of anxiety and depression in particular [36].

The clinical problem associated with the benzodiazepines is the tendency to promote tolerance, dependence, and withdrawal. This is to a lesser degree than alcohol and the barbiturates. They are relatively addictive substances. The shorter half life (triazolam) and more rapidly absorbed (diazepam) products are usually the most abused. They also promote a clinical spectrum of anxiolysis through coma. An intentional overdose is sometimes lethal in a suicide attempt especially if mixed with alcohol. Unlike ethanol and the barbiturates, there is a way to treat an overdose with a reversal agent called flumazenil [37]. On occasion, respiratory suppression and death occurs.

Benzodiazepines are easier to dose as they have more reliable pharmacokinetics, no hepatic autoinduction and metabolism, a better dose response curve, and variable but predictable halflives. These agents were the gold standard in treating anxiety from the 1960's through the early 1980's. They were extensively utilized and, as per the previous paragraphs, quite effective in lowering anxiety symptoms both acutely and chronically.

Sometimes, monoamine oxidase inhibitor or tricyclic antidepressants were used to treat anxiety. The mechanism of action was radically different in that serotonin was elevated instead of GABA. These drugs were considered second line as most clinicians favored the more benign side effect profile of the benzodiazepines over the hypertensive crises and cardiotoxicity of the antidepressants mentioned above. It was not until a selective serotonin reuptake inhibitor (SSRI) was developed and FDA approved to treat depression that clinicians were able to use a safe serotonergic agent over the GABAergic benzodiazepines. As off label use climbed and similar SSRIs were developed and studied, the age of the

GABA anxiolytic quickly faded for 15-20 years and they were moved to a clear second-line treatment option.

II. The Age of Serotonin

A. Selective Serotonin Reuptake Inhibitors

The SSRI class of antidepressants came into existence with fluoxetine in the 1980s. It was first FDA approved to treat depression. Over the next several years five other SSRIs were developed. Sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram all became FDA approved to treat major depression with the exception being fluvoxamine's obsessive-compulsive disorder indication. Predominantly, paroxetine and sertraline entered a competitive marketing campaign where studies were designed to show that either product also was able to adequately treat anxiety disorders [7]. Unlike the benzodiazepine sedative's research and development history, SSRIs were immediately studied in anxiety specific areas.

All of the SSRIs share the same mechanism of action. Neurons possess pumps that are able to recycle and move excess extracellular serotonin and move it back into the neuron to be repackaged for later use. The SSRIs block or make this pump inactive, causing serotonin to passively build up in the synaptic extracellular space. Eventually, this excess serotonin may cause intracellular changes and anxiety resolves. Typical side effects include weight gain, sexual dysfunction, sedation, tremor, headache, insomnia, agitation, gastrointestinal upset. Many are transient but the first two effects tend to be chronic while the SSRIs are continued [7].

Historically, paroxetine was the first SSRI to have multiple anxiety indications. It holds FDA approval to treat panic disorder, obsessive compulsive disorder, post traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder. Evidence is robust for efficacy of paroxetine in GAD, which has been evaluated in almost 2000 patients in placebo controlled short and long-term trials [38, 39]. Paroxetine is the SSRI most extensively studied in social anxiety disorder with positive therapeutic results [40]. A recent study reported that paroxetine in doses of up to 60 mg over 12 weeks was effective in noncombat-related PTSD. The study showed that improvement in hyper arousal and avoidance occurred over first 8 weeks, while reexperiencing of symptoms improved more gradually over 12 weeks (Marshall *et al.*, 1998) [41].

Sertraline has FDA approval to treat posttraumatic stress disorder, obsessive compulsive disorder, social anxiety disorder and panic disorder. In panic one study, 93 patients were randomized to sertraline and 90 were randomized to placebo. Discontinuation due to insufficient clinical response occurred in 23.6% of placebo-treated patients and 12.0% of sertraline-treated patients. Thirty-three percent of placebo-treated patients had an exacerbation of panic symptomatology, versus 13% of sertraline-treated patients [42].

Sertraline (50-200 mg/day) was effective and generally well tolerated in the treatment of childhood and adolescent OCD for up to 52 weeks. Improvement was seen with continued treatment [43]. Efficacy ranged from 72% in children to 61 % in adolescents.

One hundred and seventy-eight out-patients with panic disorder who exhibited at least four panic attacks during the four weeks prior to screening and three during the two weeks of lead-in were randomly assigned to 12 weeks of double-blind treatment with sertraline (50, 100 or 200 mg) or placebo. Results demonstrated that Sertraline was superior to placebo in reducing the number of panic attacks, situational attacks, unexpected attacks, limited symptom attacks, and time spent worrying [44]. Recent work with sertraline also suggests that this drug is both safe and effective in PTSD.

Fluoxetine holds FDA approval to treat obsessive compulsive disorder and panic disorder. Fluoxetine was the first SSRI approved for the treatment of OCD in the United States. In a recent review, fluoxetine was found to be effective in OCD within the dose range of 40–60 mg/day and efficacy was maintained over 3 years [36]. Relatively higher doses and longer duration of treatment may be necessary to effect a response in OCD [45].

A meta-analysis by Boyer (1995), comparing SSRIs and clomipramine and alprazolam for the alleviation of panic attacks, found that, while all the three drugs were superior to placebo, the SSRIs were superior to imipramine (generally considered the gold standard panic treatment in Europe) and alprazolam [46].

Fluvoxamine is FDA approved for obsessive compulsive disorder. It has an off label use in other anxiety disorders. Figgitt and McClellan (2000) reported that fluvoxamine 300 mg/day for 6–8 weeks was as effective as imipramine in patients with panic disorder and significantly more effective than placebo [47]. Van der Kolk *et al.* (1994) reported significant response to fluoxetine in doses up to 60 mg/day over 5 weeks, while Davidson *et al.* (1997) did not find any benefit with fluoxetine at lower doses [48, 49].

Citalopram has been FDA approved for depression and the efficacy of this medication in OCD (off label use) is about 75% at a dosage of 40-60 mgs day [50]. De Boer *et al.* studied fluvoxamine in 24 Dutch resistance fighters with chronic PTSD [51]. Modest improvement was reported on a PTSD self-rating scale with 5 of the 11 completers reporting substantial improvement. Davidson *et al.* reported similar response with fluvoxamine in civilian population.

Tricyclic Antidepressants (TCA's)

TCA's were used for all anxiety disorders and have been approved by the FDA for panic disorder. Two studies published in the 1980s found that patients suffering from a primary anxiety diagnosis but with subsyndromal levels of depression benefited from treatment with tricyclic antidepressants [52]. One hundred and seven patients with panic disorder or agoraphobia with panic attacks were studied 1-4 years after treatment with a tricyclic antidepressant. At follow-up more than 80% of the patients remained symptomatic but fewer than half were experiencing panic attacks and only 40% were avoiding phobic situations [53].

In at least 12 double-blind comparative trials, clomipramine has exhibited significant benefit in patients with obsessive compulsive disorder. In the United States, clomipramine is approved only for the treatment of obsessive compulsive disorder [54]. In a group of 17 veterans diagnosed with PTSD treated with tricyclic antidepressants,

prior to treatment, 82% were rated as markedly or severely ill and 18% as moderately ill. Following treatment, 82% were rated as much improved and 18% as minimally improved [55].

Monoamine Oxidase Inhibitors (MAOI)

The effective therapeutic dose range for moclobemide in most acute phase trials was 300 to 600 mg, divided in 2 to 3 doses. While one controlled trial and one long-term open-label study found moclobemide to be efficacious in social phobia, three controlled trials subsequently revealed either no effect or less robust effects with the tendency of higher doses (600 - 900 mg/d) to be more efficacious. Two comparative trials demonstrated moclobemide to be as efficacious as fluoxetine or clomipramine in patients suffering from panic disorder [56].

A review of 19 double-blind placebo-controlled studies in social anxiety disorder (social phobia) also showed reasonable efficacy [40]. Initial trials yielded a high degree of efficacy for phenelzine with a large difference between drug and placebo and a low rate of placebo response.

Among the reversible inhibitors of monoamine oxidase A, brofaromine may also be an effective drug, while moclobemide appears to be less potent for social anxiety disorder [57]. In addition to being effective in depressive disorders, monoamine oxidase inhibitors (MAOIs) have been shown to be effective in controlled studies of patients with panic disorder with agoraphobia, social phobia, atypical depression or mixed anxiety and depression, bulimia, post-traumatic stress disorder (PTSD) and borderline personality disorder [58]. The use of MAOI's has decreased due to their side effect profile, specifically that hypertensive crisis may occur if diet was not modified.

B. Venlafaxine

A few other agents outside of the SSRIs have gained FDA approval that are also serotonergic in nature. Venlafaxine is an agent that blocks serotonin pumps similar to the SSRIs, but it also blocks the norepinephrine pump system as well [59-61].

It is FDA approved to treat generalized anxiety disorder, social anxiety disorder and major depression. Studies suggest that Venlafaxine's effectiveness is superior to that of Buspirone for treatment of GAD [62-66]. In longer term studies, this agent allowed for 69% sustained response rates [64].

C. Buspirone

Buspirone was the first non-benzodiazepine and non-GABA agent to be FDA approved to treat generalized anxiety [67, 68]. Its approval pre-dates the SSRI approvals. This medication stimulates the serotonin 1a receptor which has been linked to anxiety states. This serotonin facilitation lowers anxiety comparably to the benzodiazepines: diazepam, clorazepate, alprazolam, and lorazepam. While it is effective in GAD, it has not been proven as effective for reducing panic attack severity and intensity [69-72].

Buspirone and gepirone (similar agent) have been used in double blind clinical trials against the benzodiazepines to confirm their effectiveness in generalized anxiety disorder.

Gepirone (not available in US) separated from placebo at week 6 and diazepam at week 1 for GAD patients but only diazepam caused temporary worsening of anxiety symptoms or rebound during taper [73]. In addition, even if effective for the control of symptoms, diazepam did not improve psychomotor performance. Buspirone has proven to be as effective an anxiolytic as the benzodiazepines. It causes less sedation and motor impairment than diazepam, and may be particularly useful in geriatric patients [74]. Similar results have been replicated with lorazepam and ipsapirone, and for lorazepam and buspirone: lorazepam acts faster but is problematic in terms of discontinuation [75-77].

III. The Return of GABA?

The advent of non-addictive and safer serotonergic anxiety medications led to the rapid under use of GABA-based benzodiazepine anxiolytics despite equal effectiveness and different side effect profiles. More recently, some GABA facilitating drugs have been used in an off-label manner (not yet FDA approved) to treat anxiety. There may be the possibility of using GABA drugs without addiction potential. It is also possible that some of these newer GABAergic agents will have a better side effect profile as well, even compared to SSRI's as they may have less weight gain and sexual function side effects.

Many of these agents are anti-epileptic in nature and have garnered FDA approval in seizure reduction. Many anti-epileptic agents have subtle to moderate effects on GABA facilitation, and it makes pharmacodynamic sense that the clinical utility of these agents would cross into the anxiolytic treatment spectrum. Unfortunately, there are few high-powered studies for these agents and data is often open-label in nature. The section below discusses the currently available information regarding these agents.

A. Gabapentin

Gabapentin is perhaps the first potential GABA facilitating medication that was studied in anxious patients. Gabapentin is now believed to be a calcium channel inhibiting agent. It has a FDA approval to treat epilepsy. It has a secondary mechanism by which GABA levels in the brain are raised. It is unclear if this medication increases synthesis of GABA or delays breakdown of GABA. Either way, mild GABA increases are detected after administration [78].

Similar to the ability of the benzodiazepine, diazepam, to alleviate both seizures and anxiety by GABA facilitation, studies that looked into gabapentin's hypothesized GABAergic nature and its ability to lower anxiety followed. Several smaller studies suggest that gabapentin may be a reasonable treatment for anxiety. In a well-powered study, treatment with gabapentin was found to be significantly more effective than placebo for the treatment of social phobia in a randomized, double-blind, placebo-controlled study involving 69 patients [79]. Gabapentin, likewise, was also shown to be effective for the treatment of PTSD in a much less powered open label, retrospective case series of 30 patients [80]. However, no significant differences between placebo and gabapentin were seen in 103 patients with panic disorder enrolled in an 8-week double-blind, randomized clinical trial, this may be a significant negative finding [81].

Megna, Iqbal and Aneja completed the most comprehensive review to date for gabapentin and have discussed some of the above data and also show data relevant to substance abuse, somatization, geriatrics and learning disabilities [82].

B. Tiagabine

Perhaps the only other current FDA approved medication with relatively higher and selective GABA potential is tiagabine. It is also FDA approved to treat epilepsy. It has a unique mechanism of action by which it elevates GABA by blocking GABA's GAT-1 re-uptake pump [83]. This mechanism is analogous to that of the SSRIs but occurs in the GABA system. Both neurons and supportive glial cells in the human brain have GABA recycling pumps. Tiagabine blocks the main GAT-1 pump and passive build up of endogenous GABA occurs. As more GABA is available, more GABA receptors are activated and more chloride is allowed in the neuron. Similar to the benzodiazepines, neuronal firing slows and epilepsy and anxiety resolves. However, the similarity between tiagabine and the benzodiazepines stops there. Benzodiazepines directly bind and alter the GABA receptors, especially after long term use. This allows for tolerance, dependence and withdrawal, the key components to addiction. Tiagabine does not bind to the GABA receptor, does not alter the receptor and has no addictive potential [84]. This medication clearly increases GABA levels and does not seem to carry the risks associated with the benzodiazepines. Tiagabine has typical side effects of asthenia, mild fatigue, headache, stomachache, lightheadedness. It has no end organ damage issues and does not require blood laboratory monitoring [83]. It does not promote sexual dysfunction or weight gain.

One positive discovery in treating the anxious patient is that tiagabine seems to promote and facilitate slow wave, restorative sleep [84]. An initial sleep electroencephalography study clearly delineated an improvement in Stage 3 & 4 delta wave sleep. Anxiety studies have shown sleep improvement as a secondary efficacy measure as well and are mentioned below.

In regards to treating anxiety with Tiagabine, several small case series have shown tiagabine to be effective in anxiolysis in a variety of disorders [85-88]. Larger, preliminary open label studies have provided initial support regarding tiagabine's anxiolytic properties. GAD, PTSD, and treatment-resistant anxiety have been studied. In a 10-week, randomized, open-label, blinded-rater trial, patients with GAD received either tiagabine or paroxetine. In this study, tiagabine was directly compared to an FDA approved serotonergic anxiety agent. Both tiagabine and paroxetine were found to reduce the symptoms of anxiety to equal degrees. Sleep measures also improved [89]. In an ongoing, 12-week, open-label study of patients with PTSD, tiagabine significantly improved all measures of PTSD in 12 subjects who had completed the study at the time of the report. Secondary sleep measures were also shown to improve [90].

Tiagabine has also been evaluated as augmentation therapy in an 8-week, open-label study of 18 patients with mixed anxiety disorders who remained symptomatic despite adequate trials of treatment with other anxiolytic therapies (78% of patients were taking SSRIs). Treatment with

tiagabine was found to significantly improve the symptoms of anxiety. Again, secondary sleep measures improved with tiagabine in this study as well [91]. All of these studies are small with low statistical power, but all suggest the possibility that tiagabine may produce an anxiolytic effect.

C. Pregabalin

The third GABA facilitating drug has not been FDA approved as yet and is called pregabalin. This agent has vague, unknown and postulated effects in the GABA system. Researchers do clearly show it to be an alpha-2-delta protein binder that slows calcium channels and reduces neuronal firing, perhaps more similar to gabapentin than tiagabine. There seems to be a downstream lowering of glutamate, noradrenaline and substance P activity [92]. Given this mechanism of action it is possible that this agent be considered as a treatment for epilepsy, anxiety, or pain.

To date, there are two well-controlled Phase III studies in press where pregabalin was used to treat generalized anxiety in a double-blind fashion [93, 94]. Pregabalin dosed between 150-600mg (divided t.i.d. dosing) provided anxiolysis. Typical side effects included: somnolence and dizziness. There is no evidence of a withdrawal symptom and there is felt to be no addictive potential to this drug. As with any potential antiepileptic drug, abrupt cessation may lead to seizure risk.

IV. Future Treatment Directions

In regards to potential new treatments for anxiety which are conceptual or in animal model testing, some interesting options may become available over time. The hypothalamic-pituitary axis has often been implicated etiologically in both depression and anxiety. Progesterone and its derivative allopregnanolone have been shown to modulate the GABA-A receptor [95]. There is an initial anxiolytic effect that then diminishes as the GABA-A receptor becomes insensitive over time. In a rat model, these investigators were able to show anxiogenic properties due to expression more alpha-4 sub-unit of the GABA-A receptor. In theory, this could lead to less ability of the benzodiazepine sedatives to create anxiolysis after administration. In translational application, newer agents could be developed to lower progesterone levels where clinical relevant to improve anxiety or at least guidelines may be issued to avoid progesterone agents in severe cases of anxiety.

The alpha-5 sub unit of the GABA-A receptor is also manipulated by an experimental compound L-655,708 in animal models and is inhibited primarily in hippocampal regions. Rats given this compound were more anxious in open-field exploration [96]. Translational research into agents that may stimulate this particular GABA-A receptor in an area often implicated in anxiety (hippocampus) is warranted.

Protein Kinase C[ν arepsilon] is a neurosteroid peptide that is also implicated in animal models to affect anxiety states. Mice genetically devoid of this peptide are generally more sensitive to GABA-A allosteric modulator (benzodiazepine) treatments. These mice also show less elevated corticosteroids which is often associated with stress, anxiety and depression. Translationally, this peptide could be

manipulated to improve anxiolytic ability of current anxiolytics, or if this peptide's levels were lowered, anxiolysis may occur [97].

The examples above also suggest that further, more specific modulation of the GABA-A receptor may result in anxiolysis. Whether this is accomplished by more specific modulation of GABA-A receptor sub-types or hypothalamic pituitary intervention remains to be seen.

CONCLUSION: IS HISTORY REPEATING ITSELF?

The authors have attempted to piece together the history of the pharmacologic treatment of anxiety. It is clear that two neurotransmitters are key to anxiety treatment, serotonin and GABA. It is also clear that there have been two eras in regards to using medications. The GABA era where the benzodiazepines were used exclusively and effectively, though with the risk of addiction and overdose. The serotonergic monoamine oxidase and tricyclic antidepressants were minimally used and minimally studied. The invention of SSRI drugs that could safely increase serotonin and did not carry addiction risk followed and largely surpassed benzodiazepine prescribing. These drugs may have been slower in regards to reaching efficacy, but carried less risk and are still considered the drugs of choice in treating anxiety. Benzodiazepines are now considered second line and used mainly for SSRI treatment resistant cases.

It is quite possible that by turning to the anti-epileptic drugs mentioned above that we may be able to once again utilize the GABA system to treat the anxious patient. Though current data is limited and clinical use is expanding, these drugs may be used in lieu of benzodiazepines when rational (poly)pharmacy is warranted and where GABA stimulation may lower anxiety symptoms. Higher level, placebo-based, studies of these agents are needed and warranted prior to first-line or widespread clinical use so that we may better treat the anxious patient to remission in a safe manner.

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