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Generalised Anxiety Disorder
Treatment Options

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Abstract

In recent years generalised anxiety disorder (GAD) has become a much better defined disorder, with specific criteria distinguishing it from the other anxiety disorders; however, it still lacks the same public and scientific interests as some of the other anxiety disorders such as panic and social phobia. Nevertheless, refinement in the treatment of GAD is becoming more evident through the conduct of clinical trials.

Up until the mid-1980's, treatment consisted primarily of benzodiazepines. However, as a result of growing characterisation of their abuse potential, other therapeutic options were explored. Benzodiazepines became seen as an effective short-term therapy, and buspirone and some of the newer antidepressants have become the treatment of choice for patients with GAD requiring long-term treatment.

Buspirone was the first available alternative to the benzodiazepines in the US; however, the initial excitement over this agent was somewhat dampened because of its mild efficacy combined with a slow onset of action. The antidepressants were seen as beneficial for the treatment of GAD because of the high comorbidity with depression, thus allowing a better outcome for these patients. The antidepressants that offer both a good adverse effect profile and efficacy are the selective serotonin reuptake inhibitors including paroxetine, and the serotonin-norepineph-

rine reuptake inhibitors such as venlafaxine. Clinicians should also consider the potential benefits of psychotherapy as an adjunct to medication.

There are a number of potentially new pharmacotherapies being investigated, including newer serotonin 5-HT_{1A} receptor agonists, cholecystokinin receptor antagonists, neurokinin receptor antagonists, gabapentin and its analogues, and γ-aminobutyric acid $(GABA)_A$ receptor modulators. However, these compounds are all in the early stages of investigation, and there are no new therapies expected to be released in the near future. Nonetheless, in the search for the ideal anxiolytic, a more positive outlook is allowed by imminent future research for new treatment options in patients with GAD.

1. Generalised Anxiety Disorder

In the Diagnostic and Statistical Manual of Mental Disorders (DSM)-II, anxiety disorders were not divided into sub-disorders, but rather included as part of a syndrome of all types of anxiety disorders and labelled as 'anxiety neurosis'. The DSM-III made a formal distinction between generalised anxiety disorder (GAD) and other anxiety disorders, but the definition of GAD was still somewhat nebulous. DSM-III-R used a more precise definition, which included specific symptoms and duration of symptoms. The definition in use today is the DSM-IV, which characterises GAD mainly by excessive anxiety and persistent worry on most days of the week for a period of 6 months or more. GAD has a 1 year prevalence rate of 3% and a lifetime prevalence rate of about 5%.[1] Among patients seen by primary care clinicians, GAD has an 8% prevalence rate, making GAD the most prevalent anxiety disorder in the primary care setting.[2]

DSM-IV criteria require that at least three (or, in the case of children, just one) of the following symptoms be present for a diagnosis of GAD: restlessness, difficulty concentrating, easy fatigability, irritability, muscle tension and disturbed sleep. The diagnosis is excluded if the focus of anxiety or worry is confined to the features of another disorder. For example, if the anxiety is based on the fear of embarrassment in public, the diagnosis would be social phobia not GAD. It is also excluded if the condition is due to the direct effects of a substance or a general medical condition, or if it occurs exclusively during a mood disorder, a psychotic disorder or a pervasive developmental disorder. Yet despite these improvements in definition, the diagnosis of GAD may be complicated by concomitant psychiatric or somatic illnesses, such as depression or other types of anxiety disorder;[3] such complications are especially problematic when treating elderly patients, whose symptoms of anxiety may be mixed with symptoms of depression, physical illness and cognitive impairment.[4]

Research on the evolution of GAD symptoms over time and their relationship to stress is needed. Stahl[5] has advocated expanding the generalised anxiety syndrome to include symptoms of mild depression, as mixed anxiety/depression (MAD). Comorbidity with substance abuse further complicates GAD diagnosis and treatment. One study of 125 males with substance abuse found that polysubstance dependent individuals were more likely to be diagnosed with anxiety disorder or bipolar disorder.[6] Another study of 425 patients with drug dependence found that these patients had a 10% lifetime prevalence rate for developing GAD, and that the majority of drug-dependent persons developed GAD after the onset of drug dependence.[7]

The clinical course of GAD is chronic and fluctuating in severity, often worsening during periods of stress. The usual age of onset is in the late teens or early twenties, however, many patients report prior symptoms of anxiety during childhood as well. In terms of gender differences, overall, females make up approximately two-thirds of patients with GAD. Males who reported four or more significant life events had an 8.5 times greater risk of GAD than did those who reported zero to three life events. In contrast, females showed no similar

association with significant life events, but both men and women who reported at least one unexpected, negative and very important life event had a 3-fold greater risk of developing GAD.[8] GAD has a relatively low rate of recovery, when recovery is defined as reduction to only one or two symptoms with a subjective sense of returning to normal. Using this definition, GAD has a 20% rate of recovery, while major depressive disorder has an 80% rate of recovery.[9] Because GAD symptoms do not follow a consistent pattern, and may fluctuate across time, long-term management of the disorder is often necessary.

2. Methodology for Clinical Trials

There are a number of methodological obstacles that need to be addressed before the anxiolytic effect of a compound can be established, and the most salient are reviewed here.[10]

2.1 Assessment Instrumentation

Anxiety is measured primarily by the use of the Hamilton Rating Scale for anxiety (HAM-A) and the Clinical Global Impression Scale (CGI), and many studies employ these scales to evaluate the efficacy of treatment options because their use satisfies regulatory requirements for efficacy evaluation.

The HAM-A, designed by Max Hamilton in 1959, was intended to measure the range of anxiety symptoms and be able to detect changes in symptoms over time. The HAM-A consists of 14 items grouped as seven psychic anxiety items: anxious mood, tension, fears, insomnia, intellectual, depressed mood and behaviour; and seven somatic anxiety items: somatic muscular, sensory, cardiovascular, respiratory, gastrointestinal, genitourinary and autonomic.[11] Each symptom is assessed according to its frequency and severity of occurrence during the course of the previous week, with a higher score indicating a greater level of anxiety. The main criticisms of the HAM-A scale are its subjective nature, as well as its bias in reflecting somatic as well as psychic symptoms. This has raised the question of whether the HAM-A scale favours medications that are effective for somatic symptoms such as the benzodiazepines, and might not be as sensitive to newer agents that primarily improve psychic symptoms. For example, in a multicentre, placebo-controlled clinical trial evaluating lorazepam and ipsapirone in 317 patients with GAD, both agents showed a significant response on the HAM-A psychic score compared with placebo at week 1. However, on the somatic score, ipsapirone (an azapirone) showed a significant difference over placebo starting at week 2 compared with lorazepam which showed a significance at week 1 over placebo.[12] In another example, agents such as buspirone, which can cause adverse effects of dizziness and nausea, might cause an increase in the ratings on the autonomic and gastrointestinal items if the person conducting the rating was unable to distinguish these from symptoms of anxiety. Although the perfect scale does not exist, a good assessment instrument needs to be valid, reliable, sensitive, and relatively easy to administer.

The CGI is an investigator-rated global scale originally comprised of three items measuring severity, improvement, and efficacy and side effects; the first two are the ones most commonly used today to measure how effectively patients are functioning and dealing with their environment. The goal of the CGI is to gain an overall sense of how the individual is doing and whether any meaningful change has occurred.[11]

2.2 Patient Selection and Diagnosis

Standardisation in diagnosis is essential and is difficult to accomplish in anxiety disorders. Unlike medical disorders, psychiatric disorders rely heavily on patient self-reporting of symptoms to make a diagnosis. Clinicians often rely on the DSM-IV criteria to make the diagnosis. Once patient selection has been made, retention of a sufficient number of patients for statistical purposes needs to be ensured, as approximately 20 to 25% of patients randomised may not complete the study. In an attempt to enrol a sufficient number of patients, studies can be conducted at multiple sites, which can

add the additional problem of site standardisation. Multicentre studies introduce an additional level of heterogeneity from patient diagnosis and enrolment, to evaluating efficacy by raters with varying levels of reliability among the different sites.

This was exemplified in a large placebo-controlled, multicentre trial evaluating the efficacy of ipsapirone versus lorazepam. In results from a single site in this study, the HAM-A decrease from baseline was significantly different in the two treatment groups compared to placebo, with a decrease of 12.9 points for ipsapirone, 11.0 for lorazepam and 5.4 for placebo.[13] However, in the multicentre study the placebo response was nearly 4 points greater, with mean decreases of 12.7, 11.7 and 9.3 points, respectively.[12] At half of the sites in the multicentre study, patients receiving a placebo did better or the same as those given a known effective treatment.

2.3 Placebo Response

Although the double-blind, placebo-controlled clinical drug trial is one of the cornerstones of psychopharmacology research, drug efficacy may be obscured by several factors such as sensitivity to psychometrics, sample size and placebo effects. Placebo effects should be a concern in placebo-controlled trials, however, such effects have not been fully investigated.[14] Placebo response is especially prevalent in patients with anxiety disorders.[15] Some factors that influence placebo response are environmental factors such as conducting research in a healing setting, reputation and expense of the treatment, or researcher expectations of patients to improve, and patient factors such as personality, expectations or biases. In addition, the fluctuating nature of GAD contributes to a placebo response in GAD studies ranging from 18 to 67%.[16] When interpreting efficacy results it is more meaningful to evaluate treatments as compared to a placebo rather than evaluating the ability of a drug to decrease the HAM-A score. A 50% decrease in the HAM-A score is not very meaningful if the placebo response is 45%. Also a change of 50% will mean something different for a patient with a large number of severe symptoms than for a patient with comparatively minor symptoms.[14]

It is important to achieve low placebo response rates in research as it confirms the overall reliability of methods, results and conclusions by providing evidence of the sensitivity of the efficacy measures used in the study. A placebo washout period at the start of trial is generally a standard requirement. In a washout period, all patients are started on a single-blind placebo administration for some period of time. Removal of responders to placebo from the study sample should, theoretically, reduce the overall placebo response rate. However, some studies do not support this theory.[17] Another very helpful strategy is to standardise data collection procedures such as adverse events reporting within a study site and ideally across all study sites in multicentre studies to ensure the reliability level of the data collected; this helps to reduce what appears to be a placebo response. One way to improve standardisation is through continued training and follow-up of procedures and techniques to establish solid interrater reliability.[14,18]

The length of the clinical trial is an important component that can also impact the results. In anxiety disorders, trials 4 weeks in length became the standard with the development of benzodiazepines, where the effect is expected to occur within 1 to 2 weeks. However, with the development of newer agents that display less immediate activity on somatic symptoms, such as muscle tension and insomnia, a 6- to 8-week trial is recommended to allow adequate time to evaluate a response.

2.4 Bridging Studies

Successful development of novel anxiolytic agents can be achieved best through the employment of bridging studies.[19-21] Bridging studies utilise patients rather than only healthy individuals in phase I to aid in defining the maximum tolerated dose. The maximum tolerated dose differs between healthy individuals and patients. For example, a patient with GAD might be able to tolerate diazepam 30 mg/day compared with a healthy individual who might sleep all day on such a dose.

This can also be exemplified in a recent bridging study evaluating lesopitron, a novel anxiolytic compound of the azapirone class. A phase I study in 100 healthy volunteers determined that a single 50mg dose, as well as repeated dose of 45 mg/day over 7 days was well tolerated. In contrast, the bridging study found that the maximum tolerated dose in this patient population was 50mg twice daily, twice as high as the highest dose evaluated in the healthy volunteers.[22]

Differences in tolerance between patients and healthy individuals has been observed in a number of disorders affecting the central nervous system (CNS) including Alzheimer's disease, schizophrenia and depression.[23-29] The reasons for these differences are not clear and may be related to pharmacodynamic differences in end organ or receptor response as well as prior exposure to medication. The use of bridging studies aids in accelerating the parameters set for phase II studies by minimising the occurrence of too low or too high dose administration, thus saving both time and money and allowing for a more confident assessment of efficacy in phase II of development.

3. Pharmacological Treatment

The main goal of pharmacotherapy in GAD is treating the core symptoms, such as chronic worry and tension, with agents that have a rapid onset of action, few adverse effects including limited potential for abuse, and which can be taken on a long-term basis to prevent relapse.

3.1 Benzodiazepines

The earliest benzodiazepine available for clinical use was chlordiazepoxide, approved in 1960, and soon followed by diazepam, approved in 1961. These agents rapidly became the treatment of choice for anxiety, replacing the barbiturates and becoming the most frequently used psychiatric class of drugs worldwide. Benzodiazepines are still the most commonly prescribed medications for GAD and are the pharmacological gold standard for treating anxiety disorders.[30]

The mechanism by which benzodiazepines elicit an anxiolytic response is by increasing the affinity of $GABA_A$ receptors for GABA (γ-aminobutyric acid), a major inhibitory neurotransmitter in the brain.[31] Clinical trials comparing benzodiazepines to placebo generally show moderate to marked improvement in 65 to 75% of patients receiving active treatment.[32] Most of the improvement associated with benzodiazepines occurs within the first few weeks of treatment. Some predictors of positive response to benzodiazepines are: acute symptoms, high levels of psychic and somatic anxiety, low levels of depression and interpersonal problems, expectation of recovery and desire for medication.[33] In long-term use, tolerance occurs to the benzodiazepine adverse effects (such as sedation), however, clinicians have noted that tolerance to the anxiolytic effect does not seem to appear.[34]

Up to 50% of patients using benzodiazepines do not relapse when treatment is discontinued after 6 weeks,[35] and thus clinicians may wish to taper and discontinue the treatment at this time in order to identify which patients can discontinue and which need to resume treatment. Long-term treatment may be appropriate for patients who begin to relapse after discontinuation of treatment.[36]

Clinicians must make a choice in deciding which of the many marketed benzodiazepines to prescribe. Dubovsky[37] argued that there is no evidence that one benzodiazepine is superior in efficacy to another or that benzodiazepines typically recommended for the treatment of insomnia are less effective in treating daytime anxiety than the ones labelled as anxiolytics. Despite their similarities, benzodiazepines do vary on a number of parameters, including lipid solubility, potency, half-life and metabolism. Lipid solubility affects the absorption of the drug into the bloodstream, its distribution in the body, and its entry and exit from sites of activity in the brain. Potency, indicated by the dosage necessary for a clinical effect, reflects in part the lipid solubility and the affinity of the drug for the benzodiazepine receptor. Half-life re-

flects how rapidly the drug is removed from the body and whether it accumulates.

Diazepam is slowly metabolised and has multiple active metabolites with long half-lives. This gives it the advantages of fewer intradose symptom breakthroughs and the ability to taper the dosage more rapidly without provoking withdrawal symptoms. However, because patients have abused diazepam, clinicians in the US are now favouring clonazepam, a high-potency benzodiazepine with a longer half-life for the parent compound. Volunteers with a history of abuse had a preferential 'liking' towards diazepam compared with oxazepam.[38] The rapid onset of action and short time to maximal effect of diazepam probably contribute to the high abuse of this agent. The more recently developed benzodiazepines (alprazolam and clonazepam) are more potent anxiolytics and have quickly grown to be more popular for treatment of anxiety. For the elderly or patients with liver disease, benzodiazepines such as lorazepam and oxazepam that undergo glucoronidation rather than extensive liver metabolism and have shorter half-lives are often preferred.

Several factors limit the use of benzodiazepines, including adverse events such as sedation, fatigue, impaired psychomotor performance, decreased learning ability, and the potential for abuse. Benzodiazepines can also aggravate depression, potentiate the effects of alcohol and cause transient global amnesia. Alcohol in combination with benzodiazepines can lead to numerous complications including drug-induced deaths, drug overdoses and traffic accidents.[39,40] In the elderly, the sedative effects can contribute to motor incoordination with increasing potential for falls and other complications. Use of benzodiazepines can lead to physical tolerance, and physical and psychological dependence (sometimes in as little as 2 weeks), and discontinuation can be followed by relapse, rebound anxiety and withdrawal symptoms. Too rapid withdrawal from benzodiazepines carries the risk of seizures, however, the use of benzodiazepines with longer half-lives might be expected to produce fewer withdrawal problems. In some patients benzodiazepines have been reported to produce disinhibitory reactions which can be manifested as aggressive behaviour. The mechanism behind this manifestation has not been fully explained, but it appears to occur more commonly in younger patients and in patients over 65 years of age.[41] Benzodiazepines have also been implicated in traffic accidents as a result of impairing reaction time and psychomotor function.[42,43]

There are two types of dependence that can occur with benzodiazepine use, psychological and physical. Psychological dependence refers to drug craving that can lead to drug-seeking behaviour, and physical dependence occurs when the drug is stopped and symptoms of withdrawal, such as rebound insomnia and anxiety, ensue.[44,45] Not all patients taking benzodiazepines develop dependence, however, the risk for developing dependence is greater for patients affected by panic and generalised anxiety disorders than other anxiety subtypes.[46] The chronic nature of GAD encourages long-term treatment, resulting in the increased likelihood of benzodiazepine tolerance.[47] Despite this, the incidence of dependence among benzodiazepine users is quite low, estimated to be around 0.01%,[48] and appears to be primarily limited to individuals who are either current or past abusers of alcohol or other substances.[37]

Symptoms of withdrawal have been observed in some patients treated with benzodiazepines after only 3 weeks of therapy.[49] These symptoms typically occur after the first week of drug discontinuation and can last up to 6 weeks. Symptoms of withdraw typically mimic symptoms of anxiety disorders and may include anxiety, insomnia, muscle twitching, unsteadiness, anorexia, and hypersensitivity to light and noise. Withdrawal symptoms are believed to occur with greater frequency and severity with prolonged use, abrupt discontinuation and with rapidly eliminated benzodiazepines.[44] Alprazolam treatment can result in rebound anxiety and withdrawal symptoms upon discontinuation; a very slow tapering schedule over a prolonged period of time is often required to avoid such symptoms.[50,51]

Another factor limiting the use of benzodiazepines is the strong bias against them exhibited by both patients and clinicians. In one study, 70% of the 3161 people surveyed, and just under 50% of those who had previously taken tranquillisers, agreed with the survey statement that such drugs 'do more harm than good'. Most participants believed that tranquillisers prevent people from working on their problems, that taking them is a sign of weakness and that physicians prescribe them too frequently.[52] This, coupled with the unfounded notion of widespread abuse, has created a negative light in which the media portrays this class of compounds, and has led to less use of benzodiazepines in recent years. Even when prescribed and monitored judiciously by conscientious practitioners, patients can obtain prescriptions from other sources and escalate their usage. For these reasons attention has focused on the use and development of other agents for treating anxiety.

3.2 Buspirone

The first and most prominent of the non-benzodiazepine anxiolytics available for the treatment of GAD was buspirone, which is a partial agonist for serotonin 5-HT_{1A} receptors in the brain. Buspirone was initially championed as a replacement for the benzodiazepines because of its favourable adverse events profile, producing no physical dependence, withdrawal or psychomotor impairment, and its lack of interaction with alcohol and potential for abuse. The impetus to find an alternative agent to replace the benzodiazepines led the US Food and Drug Administration (FDA) to overlook the somewhat weak efficacy data in clinical trials. Members of the advisory committee were presented with approximately a dozen clinical trials of which only two of the placebo-controlled studies found significant results. Nevertheless, the panel voted to approve the drug in 1986.[10] However, there have been numerous successful subsequent studies, including a multicentre, double-blind, placebo-controlled study evaluating buspirone in patients with GAD with co-existing mild depressive symptoms which found buspirone to be superior to placebo. [53]

The short half-life of buspirone, approximately 2.5 hours, led to the practice of administering it three times a day (typical maintenance dosage is between 15 and 60 mg/day), a regimen which can result in poor compliance. To aid compliance, clinicians have evaluated administering buspirone on a twice daily schedule. A clinical trial and subsequent meta-analysis evaluating twice versus three times daily administration concluded that buspirone 15mg twice daily was as well tolerated as buspirone 10mg three times daily.[54,55]

Attempts have also been made to formulate buspirone into a once daily extended-release (ER) formulation in order to ease administration. In one early clinical trial evaluating 135 patients randomised to two different dose ranges of buspirone ER, 15 to 45mg and 30 to 90mg, or placebo found no significant difference between the treatment arms. However, a subanalysis of 39 patients with higher baseline HAM-A scores (>24) found a significant difference compared with placebo for the high-dose buspirone ER formulation.[56] Additional once daily formulations are currently in development with formulations that promise to be consistent in their release properties.

Studies were also conducted on the metabolite of buspirone, 1(2-pyrimidinyl)-piperazine (1-PP), as it was suggested that the metabolite 1-PP impaired the effects of the parent drug,[57] and an attempt was made to bypass the formation of 1-PP via first pass metabolism by the creation of a buspirone patch. However, to our knowledge this approach was not successful. The effect of 1-PP on buspirone remains controversial, with some studies showing that 1-PP may also have anxiolytic properties.[58,59]

The major disillusionment with buspirone was its onset of action. Unlike benzodiazepines, for which the onset of effect is rapid, buspirone has little anxiolytic effect for at least 1 or 2 weeks, and perhaps longer.[37,60,61] Also, patients who responded well to benzodiazepines typically did not respond as well to buspirone, and this is often at-

tributed to a lack of effect on somatic symptoms.[61]

3.3 Antidepressants

GAD very frequently occurs with other mood disorders, in particular depression which is the most common anxiety-mood comorbidity, often resulting in a poorer prognosis. This observation prompted the use of antidepressants as a treatment option for both GAD and co-existing depression.[62] Many antidepressants have demonstrated therapeutic efficacy in treating symptoms of anxiety at doses similar to those used for treating major depression. Adverse events are a concern with the tricyclic antidepressants (TCAs; imipramine, doxepin), which are associated with anticholinergic effects, orthostatic hypotension, sedation, slowing of cardiac conduction, weight gain and toxicity in overdose. Many of the newer agents such as the selective serotonin reuptake inhibitors (SSRIs), including paroxetine, and the serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, have clinical indications for use in GAD and are becoming the antidepressants of choice for treating the condition. These newer agents are much safer in overdose and have a more favourable adverse event profile than the tricyclic compounds.

The first antidepressants used for GAD were the TCAs. It was found that tertiary TCAs with both noradrenergic and serotonergic properties were effective in treating anxiety.[63] However, all studies evaluating imipramine were conducted prior to the DSM-IV diagnostic criteria, and many were conducted pre-DSM-III criteria. In the 1980's Kahn et al.[64] conducted an 8-week multicentre study comparing imipramine with chlordiazepoxide and placebo. The sample consisted of 242 patients diagnosed with primary anxiety. At week 2, imipramine was found to be more effective than both chlordiazepoxide and placebo. Retrospective exclusion of patients with panic and phobia resulted in the same conclusions.

Another 8-week, placebo-controlled study conducted by Rickels et al.[65] compared imipramine, trazodone, diazepam and placebo in 230 patients with GAD (DSM-III criteria) who did not have major depressive or panic disorder. This study found that on the HAM-A scale at week 2, diazepam was significantly more effective than the other treatments evaluated. By week 3, all active medications were superior to placebo. However by week 4, imipramine was superior to diazepam, trazodone and placebo, and by week 6 it was the only treatment that retained statistically significant improvement over placebo on the HAM-A scale. The authors concluded that diazepam was effective only initially for the somatic symptoms of anxiety, and imipramine had a more sustained effect and was effective for the psychic symptoms of anxiety.

TCAs may well be effective for the treatment of GAD, but there is little incentive to further study these older drugs in large clinical trials. Additionally, the TCAs have been surpassed in their safety profiles by newer classes of antidepressants.

The efficacy of the SSRIs was first evaluated on other anxiety disorders such as social phobia and obsessive-compulsive disorder, and only recently for the treatment of GAD. One study evaluated paroxetine, imipramine and 2-chlordesmethyldiazepam over an 8-week period in 81 patients meeting the DSM-IV criteria for GAD.[66] Significant improvement from baseline was observed for all three drugs studied on the HAM-A scale. The findings derived from this study were similar to that of Rickels et al.,[65] that the benzodiazepine was more effective initially for somatic symptoms, while the antidepressant improved the psychic symptoms as well. However, an obvious limitation of this study was the lack of a placebo control. A recent placebo-controlled study was conducted evaluating paroxetine 20 to 50 mg/day over 8 weeks in 324 outpatients with GAD.[67] While a significant difference was noted on the HAM-A anxious mood item from week 1 and onward, a significant effect on the total HAM-A score was not seen until week 8.

The most recently approved antidepressant for GAD is the SNRI venlafaxine XR (extended release). Venlafaxine XR was studied in patients with GAD and GAD with co-morbid depression. Rudolphe et al.[68] completed a meta-analysis com-

bining six venlafaxine XR studies, which included 1627 patients with GAD and comorbid depression. Patients receiving venlafaxine XR were found to have a significantly higher response rate compared with placebo after the first week of treatment.

There have been a number of placebo-controlled trials evaluating venlafaxine XR in patients with GAD without depression.[69-71] One 8-week, fixed-dose study of 365 patients comparing venlafaxine XR, buspirone and placebo found a statistically significant improvement in HAM-A score in venlafaxine XR recipients compared with placebo recipients at week 8. On the CGI, venlafaxine and buspirone were numerically superior to placebo at all time points. Venlafaxine significantly decreased the severity score at weeks 3 through 8, and buspirone at weeks 6 through 8.[70] Another study conducted over a 6-month period evaluated 238 patients assigned to either placebo or venlafaxine XR. Venlafaxine XR was statistically superior to placebo on the HAM-A score starting from week 1 until the end of the study at week 28.[72] Together, these studies show venlafaxine XR is effective for short- and long-term use in patients with GAD with and without depression.

3.4 Psychotherapy

There have been various nonpharmacological therapies for GAD developed using self-control techniques and anxiety management techniques. Of these, cognitive behaviour therapy (CBT) has been most studied in patients with GAD.[73] CBT involves training the patient to detect internal and external stimuli that trigger anxiety and to apply newly learned coping skills that target the psychic and somatic symptoms of the disorder.[74]

Three studies compared CBT alone or in conjunction with pharmacological therapies in patients with GAD. Lindsay et al.[75] compared CBT, anxiety management training (AMT), a benzodiazepine or placebo in 40 patients with GAD. Assessment was measured by several questionnaires and the Zung Self-Rating Anxiety Scale. The results were that the most immediate and greatest improvements occurred in the benzodiazepine group, however, the benefits seen in this group decreased with time, while the group receiving nonpharmacological treatments made significant and consistent improvement throughout the duration of the study. The major weakness of this study was the small sample size of just 10 participants per treatment arm. A small study was conducted by Power et al.[76] comparing CBT, diazepam and placebo. Results of this study indicated that CBT was superior to diazepam and placebo. These researchers expanded the first study, studying CBT, diazepam, placebo and combination treatments of CBT plus diazepam and CBT plus placebo in 101 patients.[77] The results post-treatment and 6 months later indicated the superiority of CBT alone and in combination with diazepam. The major criticism of the studies by Power et al.[76,77] was that they used a symptom criteria of only 1 month duration, and not the 6 month duration recommended in the DSM-IV, which may limit the results from being generalised to the patient with more chronic disease.

Trials are still needed to assess how CBT compares to pharmacological treatments such as paroxetine or venlafaxine. One recommendation is to use pharmacotherapy simultaneously with psychotherapy employing coping strategies to attain a more rapid initial response.[74]

4. Future Therapeutic Options

Of late, GAD has not captured large interest from the research community, resulting in little progress being made in new therapeutic options. However, there are a number of new therapeutic classes that are being investigated as possible treatment options for GAD, including neuroactive peptides such as cholecystokinin (CCK) receptor antagonists, neurokinin (NK) receptor antagonists, newer 5-HT_{1A}-receptor agonists, gabapentin and gabapentine analogues such as pregabalin, and $GABA_A$-receptor modulators.

The present focus for novel antianxiety medications has shifted attention from the serotonin neurotransmitter systems to the role of neuroactive peptides in the modulation of anxiety behaviours.

Most clinical research to date has focused on the effects of CCK. CCK is an important neurotransmitter found in the gut but it is also distributed in the CNS. The predominate forms of CCK in the brain are CCK-8 and CCK-4. Infusion of CCK-4 peptide into animals and humans has been shown to cause anxiety and panic attacks.[78-80] CCK is mediated by two receptors, CCK_A and CCK_B. CCK_B receptors are found in high levels in the CNS, and therefore research has focused on creating CCK_B receptor antagonists.

There have been clinical trials investigating two CCK_B-receptor antagonists, L-365260 in panic disorder and CI-988 in GAD.[81,82] Although both of the drugs were well tolerated, the authors failed to detect a significant difference between drug and placebo. Kramer et al.[81,82] suggested that poor pharmacokinetics and inadequate dosage could be responsible for the poor response seen. At one of the sites evaluating CI-988, response favoured CI-988 on the HAM-A somatic score, but not on the psychic score. Overall the HAM-A decrease from baseline trended toward significance ($p = 0.06$) but because of the small sample size of 29 patients from this site a definite conclusion could not be made.[83] Further clinical trials are needed with CCK_B-receptor antagonists before any definite conclusion can be reached regarding their potential benefit in anxiety disorders.

In addition, more studies are needed to gain a better understanding of the role of CCK receptors in anxiety, since it is unlikely that CCK receptors by themselves are the final common pathway leading to anxiety, but rather CCK probably interacts with other neuronal systems causing anxiety. For example, in animals CCK appears to be co-localised with dopamine in the ventral tegmental area.[84,85]

Another group of neuroactive peptides is the tachykinins, whose action is mediated by the activation of G-protein coupled receptors. NK_1 and NK_3 receptors are extensively distributed in the CNS, while the NK_2 receptor is primarily found in smooth muscles of the gastrointestinal, respiratory and urinary tracts, and to a lesser extent in the CNS. Several NK_1- and NK_2-receptor antagonists have been identified and investigated in animal models of anxiety. NK_1-receptor antagonists, such as CGP-49823 and NKP-608, have been shown to have an effect in the rat social interaction test,[86,87] and CGP-49823 increased social investigation in gerbils.[88] NK_2-receptor antagonists GR-159897 and saredutant (SR-48968) have been reported to have an anxiolytic-like effect in rodents, significantly increasing the time they spend in front of a cage following a threat, an event that is consistent with anxiolytic-like action.[89] These data might suggest that NK receptor antagonists might have a role in GAD, however, findings have been variable and some have shown contradictory effects in other anxiety models suggesting the need for further investigation. There are currently no published human data on NK receptor antagonists in GAD, however, in a previous study of an NK_1-receptor antagonist in patients with depression and moderately high anxiety, a significant response on the HAM-A was observed.[90]

The introduction of buspirone in 1986 sparked the development of other 5-HT_{1A}-receptor analogs such as gepirone, ipsapirone, lesopitron and tandospirone in efforts to improve on the efficacy of buspirone. Some researchers believe that magnitude of the effect is related to the ligands ability to bind to the 5-HT_{1A} receptor, which would explain the relatively poor efficacy of some of these agonists.[91] This idea has lead to the development of compounds such as flesinoxan currently in phase III, and eptapirone (F-11440), both of which have high affinity for the 5-HT_{1A} receptor binding site. However, to date no compound that acts on the 5-HT_{1A} receptor site, other than buspirone, has come to market as a treatment for GAD, although gepirone is currently in late stages of development as an antidepressant and indeed, buspirone itself appears to have antidepressant effects.[92]

Some attention has also focused on developing compounds that bind to other serotonin receptors such as 5-HT_2. The 5-HT_2 receptor antagonist fananserin (RP-6220) has produced anxiolytic effects in animal conflict tests.[93] Another 5-HT_2–re-

ceptor antagonist glemanserin (MDL-11939) was evaluated against placebo in 72 male patients with GAD (DSM III-R criteria). Although all measures showed trends favouring glemanserin, no significant changes from baseline compared with placebo were observed.[94]

Gabapentin, an anticonvulsant with a mechanism of action that has not been precisely elucidated, has been studied in panic and social phobia. Its pharmacological response is believed to be due to its interaction with GABA receptors and high affinity binding to the $\alpha 2$ subunit of voltage-activated calcium channels among other potential mechanisms. Gabapentin has not been studied in patients with GAD but results from other anxiety disorder studies were equivocal as to its efficacy.[95] Pregabalin is a novel compound structurally similar to GABA, but with negligible affinity for GABA receptors, that binds to the $\alpha 2\delta$ subunit of voltage dependent calcium channels (VDCC) with high affinity and selectivity.[96] In a rat conflict test and an elevated X-maze test, pregabalin was found to produce anxiolytic-like effects.[97] Although data on pregabalin is limited, this study points to a role for VDCC in anxiety.

In an attempt to create a benzodiazepine-like compound without the unwanted adverse effects of its class, different chemical entities that act at or near the GABAA receptor site have been identified. These compounds are of the cyclopyrrolone group and the earliest ones identified are zopiclone and suriclone. They have similar properties to the benzodiazepines, including sedative, anticonvulsant and anxiolytic activities, and have demonstrated effective hypnotic and anxiolytic activity in animal and human studies.[98,99] Other novel and more selective compounds within the cyclopyrrolone class with minimal sedative and muscle relaxant properties are currently being investigated in animal and human models. A study evaluating four doses of suriclone (0.1, 0.2, 0.3 and 0.4mg three times daily), diazepam (5mg three times daily) and placebo in 330 outpatients with GAD found that active treatments showed significant improvement over the placebo group on the HAM-A and CGI scales. The number of adverse events, such as drowsiness, were significantly higher with diazepam than with suriclone.[100] Further studies with this compound are still needed.

Several partial agonists for the GABAA receptor site have also been developed with anticonvulsant/anxiolytic activity but without the muscle relaxant-effects of the classical benzodiazepines; however, no published data exists on these compounds in humans.[101-103]

5. Discussion

While GAD and the other anxiety disorders have become better characterised in recent years, the diagnostic nosology relies primarily on the phenotypic expression of symptoms and clearly an understanding of the underlying neurobiology is required to differentiate GAD from other anxiety and mood disorders. Although the ideal anxiolytic does not yet exist, there are now a number of effective treatment options available which can be used as appropriate to the clinical situation.

Benzodiazepines are still very useful for the rapid control of acute symptoms, but for many reasons buspirone and the newer antidepressants offer a better option for patients requiring long-term treatment. Clonazepam has recently become widely used, and while it has high potency and a somewhat slower absorption than diazepam (giving less of the 'buzz' effect which can contribute to abuse) making it attractive for acute use, we prefer the intermediate half-life drug lorazepam which does not undergo liver metabolism. A very realistic concern with all benzodiazepines remains their potential for abuse and their dangerous interaction with alcohol.

The choice for long-term management can be made between buspirone and the newer antidepressants, based primarily on their respective adverse effect profiles and the prior response of the patient to such agents. As GAD is most often treated today by primary care practitioners, the SSRIs and SNRIs offer attractive treatment options as many of these agents do not require careful titration, have a simple administration schedule (i.e. once daily),

and treat a wide spectrum of anxiety and depressive symptoms.

Although none of the new agents in clinical trials would appear to offer a breakthrough in the treatment of GAD, continued and careful research on many fronts should expand our knowledge of the disorder and refine our treatment strategies for GAD.

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