Prospects for anxiolytic therapy: a reflection from different viewpoints

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Benzodiazepines are the most commonly used and effective treatment of symptoms of anxiety, but they have drawbacks. The current challenge is to discover partial agonists that do not cause the adverse effects characteristic of benzodiazepines. The authors discuss the main drugs that are used in the treatment of acute anxiety and some of the current or future alternatives and also highlight several problems that need to be resolved in the development of new anxiolytics.

Benzodiazepines are effective in the treatment of all symptoms of anxiety by acting on specific receptor sites and other agents are also able to modify the structure and activity of these receptors. Some serotonergic agents have shown some effects on anxiety symptoms, and other drugs, such as cholecystokinin antagonists, might also be useful. However, several problems need to be resolved in the development of new anxiolytics: the high placebo response rate in almost all anxiety disorders, the difficulties in characterizing anxiety, the frequent comorbidity with other mental disorders, and the need to take into account acute and long-term treatment of anxiety.

This article reviews current approaches to the concept of anxiety and its pharmacological treatment. After an attempt to distinguish physiological anxiety from pathological anxiety, we discuss the main drugs that are used in the treatment of acute anxiety and their current or future alternatives. The difficulties in characterizing anxiety disorders are stressed and the different approaches that might contribute to a better knowledge of these disorders are surveyed.

Challenge of anxiety

For many decades, most psychiatrists considered anxiety as a psychopathological dimension that presupposed a continuum of severity 'ranging from normal fears and tensions through mild to moderate levels of responses to stress and anxiety neurosis and finally to severe states such as agoraphobia'[1].

Anxiety is an emotional condition that is experienced by all humans and is characterized by an unpleasant and diffuse sense of apprehension, usually accompanied by autonomic symptoms such as headache, palpitations, mild stomach discomfort, restlessness and urinary frequency – features that tend to vary from person to person. It is quite usual to distinguish fear and anxiety; both are alerting signals that warn of danger and enable a person to take measures to deal with a threat. Fear is considered to be a response to a threat that is known, external and defined, whereas anxiety relates to a threat that is unknown, internal and vague, the main difference being the acuteness of the fear as opposed to the chronicity of anxiety.

According to the psychodynamic view, the distinction between fear and anxiety is difficult to make because fear could also relate to an unconscious, repressed, internal object that is displaced to another object in the external world. Freud suggested considering anxiety as a signal arousing the ego to take defensive action against pressures from within. Ideally, the use of repression alone results in

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the restoration of psychological balance; when repression is unsuccessful as a defence, other defence mechanisms might occur, causing symptoms that display the classical picture of neurotic disorder[2].

Considered basically as warning signals, anxiety and fear can be seen as the same adaptive emotions, warning of threats of body damage, pain, feeling of helplessness, poor social performance and ultimately of threats to one's wholeness. In response to these warning signals, people adopt behaviours or attitudes that are sufficient to prevent the threat or to minimize its consequences. Whether an event is perceived as stressful depends on the nature of the event and on the person's resources, psychological defences and coping mechanisms. A person who functions properly will be able to cope with the stressful situation and to act on external events or on internal cognition.

As soon as anxiety or fear cease to play an adaptive role, and the resulting imbalance continues for long enough, people experience pathological anxiety. During the 1960s and 1970s, this concept of an anxiety continuum was challenged by clinicians in Europe and the USA. As early as the 1960s, the efficacy of antidepressants, especially imipramine, in preventing panic attacks led to the concept of 'the anxiety equivalent of depression'. First, Klein[3] proposed that 'anxiety neurosis' should differentiate panic disorder (PD) from other forms of anxiety. Since then, other categories have been defined, such as generalized anxiety disorder (GAD), phobias (P), social phobia (SP), obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD)[4].

Different types of anxiolytics

Clinical trials have shown that the effectiveness of some drugs depends on the nature of the anxiety disorder. It is current opinion that imipramine and high-potency benzodiazepines (BZDs), such as alprazolam, are effective for PD, and that GAD should be treated with BZDs and, more recently, with 5-hydroxytryptamine (5-HT_{1A}) agonists. Moreover, nonselective monoamine oxidase inhibitors (MAOIs), either reversible or non-reversible, are useful in SP and P, and serotonin reuptake inhibitors (SRIs) in OCD. Antidepressants, particularly MAOIs, are effective for PTSD (Ref. 5).

Benzodiazepines (BZDs)

Despite the discovery of newer categories of drugs, BZDs (Fig. 1) have remained an effective treatment for many symptoms of anxiety, such as physical reactions and excessive worry. They can be defined as drugs having a high efficacy for the symptoms of anxiety and a low toxicity, with no relevant specific organ toxicity after prolonged intake even when used extensively for more than 30 years.

In the 1970s, BZDs were shown to enhance GABA transmission. Later, some specific binding sites for BZDs were identified in the brain. Recently, some molecules such as β-carbolines have been considered as possible endogenous ligands of BZD receptors[6].

Many studies have shown the effectiveness of BZDs in the treatment of pathological anxiety. Until the end of the 1980s, studies were conducted with many patients suffering from anxiety, regardless of the features of the symptoms. Since the publication of DSM-III, divisions into the various anxiety disorders have been made, allowing a more specific evaluation of the therapeutic effects of anxiolytics.

GAD has been one of the main disorders to be treated with BZDs. According to different studies, the response rate varies between 65 and 75%, with the therapeutic effect

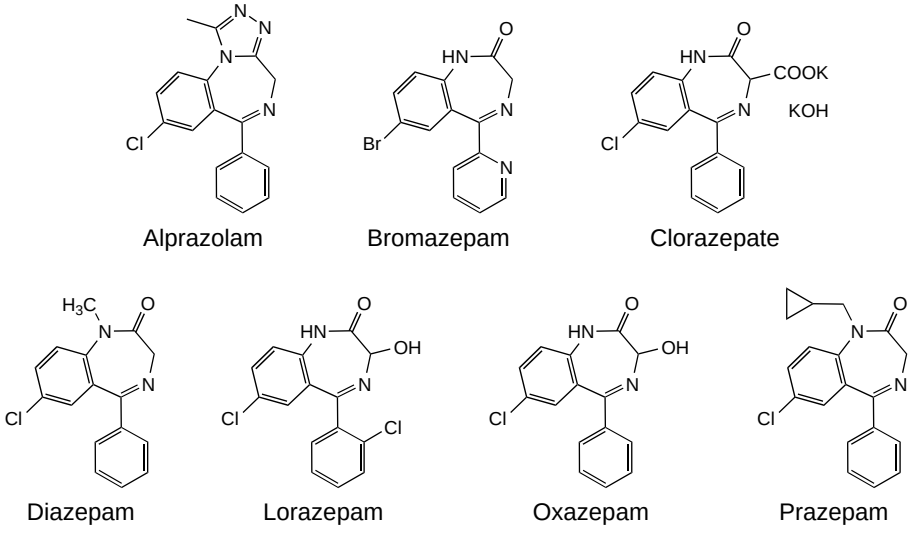

Figure 1. *Benzodiazepines are the most commonly used anxiolytics and hypnotics.*

starting during the first week of treatment[7]. Some clinical aspects can predict a good response to BZD: high intensity of anxiety, few depressive symptoms, onset of efficacy within the first week of treatment, positive relationship between patient and physician, positive opinion of the physician regarding the drug, no previous treatment prescribed. BZDs have also proved effective in some more specific anxiety disorders such as P and PD[8–10].

In France, 80% of BZDs are prescribed by general practitioners, and 10% of the population are thought to consume BZDs regularly. In principle, BZDs are prescribed for a short duration in acute conditions, with some limits that are quite difficult to define. The recommendations of the World Health Organization (WHO)[11] propose that 'for more chronic problems… a long term treatment is often necessary'. This apparent contradiction illustrates the difficulty in defining the prescription guidelines for this type of drug.

The significant consumption of BZDs in France, compared with other developed countries[12], has raised many questions concerning their suitability for treating anxiety appropriately. Their propensity to cause side effects, such as lack of alertness and motor impairment, loss of memory and other cognitive disabilities, has been shown, as well as the risk of dependency after long-term use. Moreover, specific effects such as idiosyncratic rage and depressive reactions have been indicated. These various adverse effects of BZDs need to be carefully considered.

Motor impairment. Markku *et al.*[13] showed that 10 mg of diazepam induced psychomotor impairment in both healthy volunteers and anxious patients. It is correct to highlight that BZDs can cause alterations of motor function; however, psychomotor performance could already be impaired in patients suffering from a high level of anxiety. These effects concerning motor function have been considered as risk factors for road and industrial accidents, particularly in view of studies showing significant BZD blood levels in people causing accidents[14]. However, some discrepancies do exist; for example, in the study of Girre *et al.*[15], 9.6% of the injured persons in France were BZD positive, which corresponds to the percentage of people using BZD in the general population. On the whole, the contribution of BZD in road accidents remains unclear.

Cognitive impairment. Cognitive alterations due to BZDs also need to be considered, although anxiety itself could impair memory and cause some important disablements in cognitive processes. Some authors have suggested that there might be a tolerance to the memory-impairing effects of BZDs. Certainly, the differences that might exist between the different types of BZDs need to be considered. For instance, a study by Sellal *et al.*[16] comparing lorazepam with diazepam stressed that differences in amnestic effects might occur. It appears that, while diazepam impairs free recall but spares word completion, lorazepam alters both functions and has an effect on the whole implicit and explicit memory.

Idiosyncratic rage. Although BZDs are known for their ability to reduce anxiety, they have caused some rare paradoxical increases in anxiety and overt rage response episodes[17]. This phenomenon is likely only to concern patients with poor impulse control. Some authors believe that chronic, high-dose use could worsen the mood component of depression.

Abuse reliability. The main effects that justified some legal constraints in BZD prescription (October 1991 in France: upper prescription duration limited to 12 weeks for anxiolytics and four weeks for hypnotics) are psychological and physical dependency (withdrawal symptoms after interruption of treatment) and tolerance (need to increase the dose to obtain the same pharmacological effect). Evidence of dependence related to the use of BZDs started in 1980. In 1983, Rickels *et al.*[18] and Tyrer[19] concurrently published studies in which dependence to diazepam was observed in 43% and 44% of patients, respectively. Later, the ability to be dependent on low doses of BZD was highlighted. Currently, experts agree to consider that dependence occurs with 10% of the patients on BZD prescription lasting for less than one year and between 25% and 50% if the treatment lasts for more than one year[20]. Balter *et al.*[21] brought together a committee of international experts on the pharmacotherapy of anxiety coming from 44 countries. This clinician–researcher cohort concluded that strict and differential restrictions on the use of BZDs are not justified, considering that the relative abuse liability of BZD is low and that qualitative differences in abuse liability among the BZDs are minimal[8]. Finally, BZD abuse is frequent among previously known narcotics abusers; indeed, up to 40% of narcotics abusers could be BZD abusers and probably more with some specific drugs like chlordiazepoxide and lorazepam. According to data of the WHO[11], only a small percentage of people suffering from

substance abuse mention BZD as their primary drug; moreover, withdrawal symptoms are likely to concern ~30% of the population and would occur in patients who abruptly stopped their BZD treatment. However, the occurrence of withdrawal reactions does not necessarily imply dependence. Dependence is fostered by daily dose and, probably, association with alcohol. The duration of use, the dose and individual susceptibility interact in the development of low-dose physical dependency.

In France, the use of BZDs has increased greatly since the 1970s, although for the past two years consumption appears to have plateaued. According to statistical analysis, consumption of the main BZDs (alprazolam, bromazepam, clorazepate, lorazepam, oxazepam, prazepam, diazepam) reached a peak during 1990–1992, then decreased markedly in 1995 – a period corresponding to the introduction of the RMO (legal prescription rules used in France) – before stabilization during the past two years[22]. Now a prescription for a patient cannot be for more than three months, although in some cases the prescription might need to be extended. The most recent BZD to be marketed in France was alprazolam, but it does not have any official specific indication such as depression or PD.

Alternatives to BZDs

To avoid the side effects of BZDs, researchers have searched for other drugs with the same therapeutic properties as BZD but without such important side effects. In the past few years no BZD alternative has been approved for clinical practice except alpidem[23], which was taken off the market when it led to liver toxicity that was higher than with BZDs. Also, the development of suriclone, a cyclopyrrolone, was stopped because some studies failed to demonstrate its superiority in GAD compared with placebo.

β-Carbolines. A recent development has been the discovery of partial agonists that should not cause the side effects of BZDs. Of these, abecarnil was chosen for its original activity profile, showing in animal models of anxiety a therapeutic effect superior to that of diazepam, an anticonvulsant activity and the ability to induce less dependence than diazepam.

Ballenger *et al.*[24] conducted the first reported controlled trial of abecarnil in the treatment of 120 patients suffering from GAD. The original design was for an initial group to receive 15–30 mg day^{-1} or placebo, and if this range was well tolerated a second group would receive 30–60 mg day^{-1} or placebo and a third group 60–90 mg day^{-1} or placebo. Unfortunately, because of the high incidence of CNS side effects, the protocol was changed and two other dosages, of 7.5–15 mg day^{-1} and 3–9 mg day^{-1}, were studied. Although the two higher dose groups suffered a high incidence of adverse sedative effects, causing many patients to drop out of the study, the 3–9 mg day^{-1} group was slightly improved compared with the placebo group. Since then, to our knowledge, the development of abecarnil has not progressed.

Drugs acting on serotonin (5-HT) receptors. Another area of interest is the serotonergic system. Agents that have shown some effects on anxiety symptoms include 5-HT_2 antagonists, 5-HT_3 antagonists and drugs acting on 5-HT_1 receptors (Fig. 2).

5-HT_{1A} agents, especially the azapirone group, have been developed in the past ten years in the field of anxiety. Buspirone is the only drug to be marketed, although others such as gepirone and ipsapirone have shown preliminary efficacy. Their anxiolytic effect is mediated through partial agonist activity at pre- and post-5-HT_{1A} receptors, where buspirone is hypothesized to modulate 5-HT transmission; agonist effects at presynaptic autoreceptors could temporarily reduce 5-HT concentrations, thus having anxiolytic effects. Compared with BZDs, these drugs cause less sedation, less motor impairment and less loss of memory, and do not appear to cause withdrawal syndromes clinically[6]. However, they do not appear to be as consistently effective as BZDs in patients with GAD. Moreover, they do not seem to stop panic attacks, and are less likely to help patients previously benefiting from or exposed to BZD (Ref. 25). Some non-azapirone 5-HT_{1A} receptor agonists are in the early stages of development and need further evaluation.

5-HT_2 blockers could also have anxiolytic effects, according to some recent clinical trials. Carpipramine has been marketed in France as a specific drug acting on the dimension of inhibition in schizophrenia, and subsequently for the inhibition dimension in anxiety disorders. This indication has been affirmed by a study of Ferreri *et al.*[26], which showed some effect on the anxiety dimension in patients suffering from chronic anxiety disorders, phobic disorders and adjustment disorders according to DSM-III (*Diagnostic and Statistical Manual of Mental Disorders*, 3rd

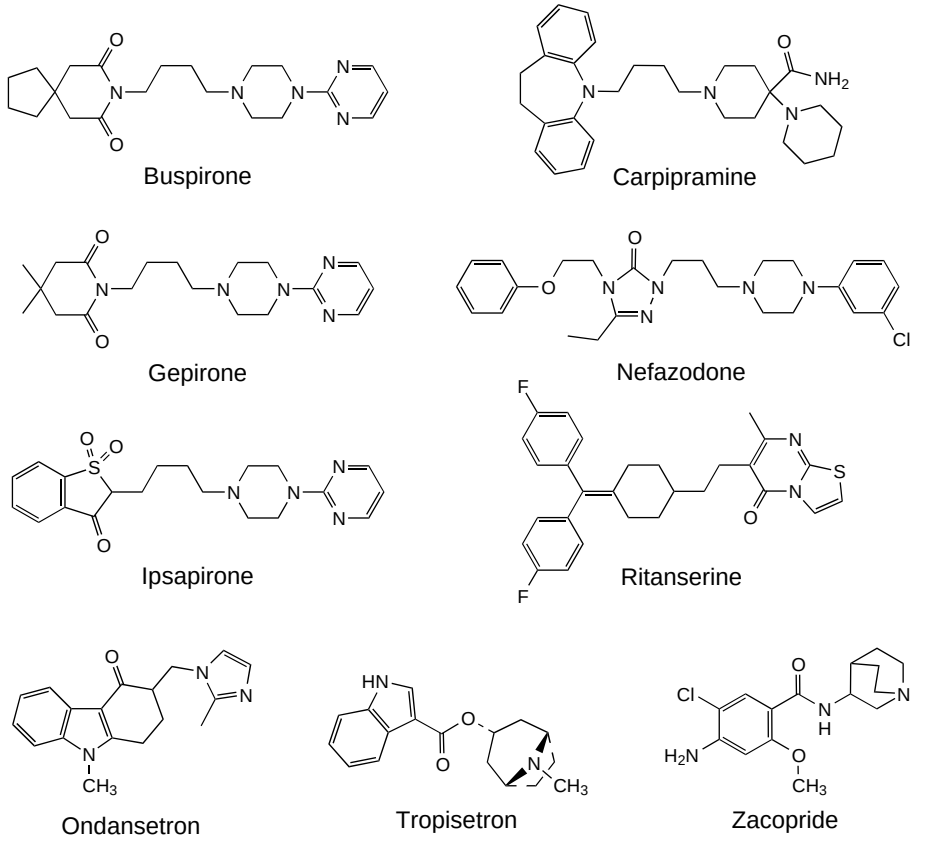

Figure 2. *Drugs that act on serotonin (5-HT) receptors have been proposed as alternatives to benzodiazepines, they include, 5-HT$_{1A}$ partial agonists (buspirone, gepirone and ipsapirone), 5-HT$_2$ blockers (carpipramine, nefazodone and ritanserine) and 5-HT$_3$ blockers (ondansetron, tropisetron and zacopride).*

edn) criteria. Ritanserine is the drug that has been studied most. It should have a rapid effect on anxiety symptoms, associated with some effects on sleep anomalies (slow waves), which might be useful in the treatment of insomnia. Some comparative studies versus placebo[27] and lorazepam[28] have indicated some significant efficacy, but it has not yet been marketed. A derivative drug, serazepine, might also prove to be effective for GAD[29]. Some drugs, such as nefazodone, that are marketed as antidepressants might also have valuable therapeutic effects on anxiety, but further studies are needed to support this[30].

5-HT$_3$ blockers have been investigated as potential treatment for GAD (ondansetron, tropisetron, zacopride) and PD (ricasetron). Preclinical data have shown that 5-HT$_3$ receptors might mediate cholecystokinin (CCK) release. In animal models this mechanism would predict an anxiolytic effect. In clinical trials, Lader[31] reported a multicentre study in which 402 patients suffering from GAD were treated by ondansetron (10 mg three times a day and 4 mg three times a day) versus diazepam (2 mg three times a day) versus placebo for four weeks. On the Hamilton Anxiety Scale, the placebo response was 45%, whereas on the CGI (Clinical Global Impression) the improvement rates were 50% with ondansetron 10 mg three times a day, 43% with ondansetron 4 mg three times a day, 48% for diazepam and 38% with placebo. Another randomized double-blind placebo-controlled study was carried out with tropisetron in the treatment of outpatients with GAD (Ref. 32). A significant anxiolytic effect was seen by day seven. Generally, the potential advantages of 5-HT$_3$ blockers would be a faster action than other 5-HT blockers (because the 5-HT$_3$ receptor would function as an ion channel receptor) and the absence of cognitive and psychomotor impairments, without any withdrawal symptoms or dependence. However, as Greenshaw and Silverstone[33] stress, there have as yet been no signs of strong contenders in this group of drugs for the clinical management of anxiety disorders.

Drugs acting on cholecystokinin (CCK) receptors. There are data to suggest that some CCK neuropeptides (e.g. pentagastrin, the synthetic analogue of the CCK-4 tetrapeptide) could be mediators of anxiety symptoms. Animal models suggest that anxiogenic effects would occur with CCK-8 (CCK-4) metabolites, probably mediated by both CCK$_A$ and CCK$_B$ receptors in the brain[34]. BZDs could antagonize CCK excitation of the hippocampal neurones. Anxiogenic properties of CCK-4 have been observed in normal volunteers and patients with PD (Ref. 35), followed by improvement with lorazepam and possibly

imipramine used as a preventive agent. Devazepide, a non-BZD CCK_A receptor antagonist, could also have some anxiolytic properties.

Other drugs. Some anxiolytic properties have been explored in other ways with neuropeptide Y (Ref. 36) and corticotrophin-releasing factor (CRF) antagonists[37], but the stage of clinical application has not yet been reached.

Problems in the development of new anxiolytics

The various types of anxiety disorders listed in DSM-III-R are summarized in Table 1, together with their definitions and current pharmacological treatments. Some new categories of anxiety disorders have been introduced in DSM-IV (Ref. 38):

- Agoraphobia without a history of panic disorder.
- Acute stress disorder, in which the person has been exposed to a traumatic event and subsequently presents symptoms such as recurrent images, thoughts, dreams and illusions that do not last more than four weeks.
- Anxiety disorder resulting from a general medical condition or a substance-induced anxiety disorder.

These categories are useful for the development of new anxiolytics. Indeed, clinical trials have shown the specific effectiveness of some drugs depending on the nature of the anxiety disorder during short- and long-term treatment of the disorder: imipramine or alprazolam in PD, selective or nonselective MAOIs in SP, selective SRIs (SSRIs) in OCD, BZD or buspirone in GAD, tricyclic antidepressants or MAOIs in PTSD.

Despite the efforts of clinicians to define more precisely the different categories of anxiety, there are still limitations in the development of new anxiolytics. These are discussed below.

High placebo response rate

One of the main difficulties in studies of new anxiolytic agents in patients with abnormal anxiety is the high placebo response rate[39]. The placebo response rate in patients with GAD is around 60%, while with patients suffering from PD or phobias the placebo response ranges up to 35%. In PTSD and SP, placebo responses rates are about 25%. A lower placebo response rate of 4–7% is observed in patients suffering from OCD. The same situation might occur in studies including depressive outpatients.

The high placebo response rate reduces the difference between pharmacological and nonpharmacological agents[40]. It also makes it more difficult to reach statistically significant differences in placebo-controlled studies, which

Table 1. DSM-III-R classification of anxiety disorders

Disorder	Definition	Pharmacological treatment
General anxiety disorder	Excessive anxiety and worry occurring most of the time, lasting more than 6 months	Benzodiazepines; buspirone
Panic disorder (with or without agoraphobia)	Four panic attacks occurring within 4 weeks; or one or more attacks being followed by a prolonged period of persistent fear of having another one	Imipramine; alprazolam; selective serotonin reuptake inhibitors; monoamine oxidase inhibitors
Phobia	Fears provoked by a specific object or situation	Monoamine oxidase inhibitors
Social phobia	Fears related to some particular situation, such as being confronted with unfamiliar people, thinking that it could cause humiliating or embarrassing behaviour	Monoamine oxidase inhibitors; (only open trials conducted with selective serotonin reuptake inhibitors)
Obsessive compulsive disorder	Obsessions or compulsions that are strong enough to cause distress	Clomipramine; selective serotonin reuptake inhibitors
Post-traumatic stress disorder	Symptoms such as re-experiences, emotional numbness, increased arousal, all persistent for at least 1 month; a delayed onset is possible and can lead to disruption of daily life	Tricyclic antidepressants; monoamine oxidase inhibitors
Adjustment disorder (with anxious mood)	Inappropriate stress reaction that did not last more than 6 months	Benzodiazepines

might influence some companies and private research teams afraid of failing in the development of their drug. It also raises the question of better identification of patients who might benefit from pharmacological treatment.

Difficulties in characterizing anxiety: the example of GAD

Numerous difficulties are encountered in characterizing of the concept of anxiety. GAD is likely to affect 4.1–6.6% of the general population in terms of lifetime prevalence[41]. Patients report having symptoms of anxiety before GAD occurs. With therapeutic support, either psychotherapy or BZD, a good short-term outcome is frequently observed, with 42% of patients showing improvement at six months[42].

A major problem is the association of GAD with personality disorders. As Tyrer[43] suggests, the fact that symptoms change over time would indicate that the diagnosis of GAD is inappropriate and that it should be replaced by the concept of general neurotic syndrome. In fact, before the release of DSM-III-R in 1987, GAD was considered a residual diagnosis. Between DSM-III-R and DSM-IV, the criteria have been revised to take account of the lack of diagnostic reliability[44].

The treatment of GAD basically comprises a combination of psychotherapy, pharmacological treatment and support therapy. It is generally considered that GAD is more resistant to treatment than other anxiety disorders. BZDs should be superior to buspirone in cases with a predominance of somatic symptoms[42]; 70% of patients respond to BZDs but two-thirds of them complain of residual anxiety symptoms, suggesting that buspirone or imipramine should be tried. Nevertheless, although long-term drug therapy appears to have some efficacy, the appropriate duration of maintenance therapy for GAD is not known[45].

One important question is whether GAD should be considered as a personality trait or as a mental state. In favour of the hypothesis that anxiety is a trait, its early and gradual onset, the fluctuation of its symptoms and the high frequency of psychiatric comorbidity indicate the co-occurrence of this disorder with other mental problems.

The problem of comorbidity

Studies examining the reliability of diagnosing GAD according to DSM-III-R criteria have shown that it is one of the disorders with the lowest diagnostic agreement. GAD is the most frequently assigned diagnosis in patients with another anxiety disorder or suffering from mood disorder. On the other hand, when GAD is the main diagnosis, it is associated with the highest rates of comorbidity[44]. As regards to the low discriminant validity of the GAD diagnosis, some authors have suggested that GAD might be better classified in DSM-IV as a disorder in need of further study.

According to studies by Brown and Barlow (reviewed in Ref. 44), 82% of patients presenting a diagnosis of GAD present at least one additional diagnosis. This means that pure GAD is rare and helps explain the lack of diagnostic reliability. For example, in the studies by Brown and Barlow[43] and Brawman-Mintzer *et al.*[46], the most frequent additional diagnosis in patients with GAD was SP (23% and 29%, respectively), while in the study by Noyes *et al.*[47] the most common additional diagnosis was simple phobia in 32% of patients suffering from GAD.

These high comorbidity rates are not unique to the diagnosis of GAD; indeed, in cross-sectional comorbidity studies, 50% or more patients with a main diagnosis of anxiety disorder would have at least one additional diagnosis. For example, 73% of patients with PD with agoraphobia are assigned at least one additional diagnosis[44].

The comorbidity of anxiety with depression also has a high frequency. Brown and Barlow[48] noted that 18% and 11% of patients with GAD had an additional diagnosis of dysthymia and major depression, respectively. Noyes *et al.*[47] found that major depressive disorder co-occurred less frequently with GAD than with PD. However, both Massion *et al.*[49] and Noyes *et al.*[47] found high rates of comorbid major depression with GAD.

Rickels and Schweizer[50], comparing depression and anxiety, proposed the concept of 'double anxiety' as an equivalent of double depression, which associates a 'chronic low-grade depression or dysthymia upon which are superimposed episodes of major depression'. Until now it has been suggested that milder forms of GAD tend to be of shorter duration and are situationally triggered. Recent epidemiological research by Wittchen *et al.*[51] suggests that milder forms of generalized anxiety tend to be fairly chronic. For Rickels and Schweizer[50], many anxious patients suffer from low-grade anxiety for a long time, and seek treatment when confronted with an acute exacerbation. This new concept should be taken into account in further research.

Chronicity of anxiety disorders and treatment?

The above concept leads spontaneously to the question of the chronicity of anxiety. Apart from acute stress disorders,

all anxiety disorders from DSM-IV should be considered as chronic illnesses.

Evidence for the chronicity of anxiety disorders comes from cross-sectional studies and retrospective assessments of duration of illness. For GAD, an epidemiological catchment area (ECA) study reports a median age of onset in the early twenties, 40% of the patients reporting a duration of illness of longer than five years[41]. For PD, according to an ECA community survey, the median age of onset was 23 years and the mean duration of the disorder was 7.1 years. Treatment studies found a mean duration of illness in the range 5–12 years. The course of panic disorder appears to be chronic, with many patients reporting periods of remission lasting six months or more[52].

Even though many drugs have proved efficacious in the short-term treatment of anxiety disorders, it is more difficult to postulate the same effectiveness beyond six months of treatment. Controlled trials demonstrated that high-potency BZDs such as alprazolam are effective in PD, as well as some antidepressants, especially imipramine, and probably MAOIs and SSRIs. Only a few studies examined the outcomes of such treatments after a follow-up of one to three years: according to a follow-up study conducted by Nagy *et al.*[53], approximately 50% or more of acute patients had a recurrence, and at least 50% resumed treatment either with a BZD or an antidepressant. On the whole, relapse appears to be the rule rather than the exception.

To avoid the side effects of long-term treatment with BZDs, including loss of attention and memory and psychomotor and cognitive alterations, current treatment consists in treating patients with imipramine for at least one year, together with behavioural and cognitive therapy, which have also proved to be efficacious[5]. A relapse will be followed by a resumption of the previous effective treatment.

For GAD, the long-term treatment strategy appears less clear than for PD. On the one hand, azapirones appear to be more reliable than BZDs. Indeed, patients treated with buspirone for six months were less likely to suffer a relapse during a three-year follow-up than those treated with clorazepate[54]. On the other hand, 60–80% of GAD patients treated for a minimum of six weeks with diazepam required additional treatment within a year. No data are available for patients suffering from GAD and treated with antidepressants. Finally, a combination of pharmacological treatment with psychotherapy (cognitive therapy and anxiety management therapy) might be effective in sustaining improvement.

What is the evidence that continuation therapy is effective in preventing relapse? There are only a few studies available on this issue. Schweitzer *et al.*[55] conducted an eight-month controlled study of continuation therapy for PD with alprazolam and imipramine and found sustained efficacy for both compounds with no dose escalation, suggesting an absence of tolerance to the therapeutic effect. At one-year follow-up, 30% of patients had a recurrence of their panic attack and 49% had restarted or never stopped their medication. For GAD, two studies seem to confirm the efficacy of BZD and buspirone as maintenance therapy over a six-month period[18,54]. In both studies, about 25% of patients experienced a return of their initial anxiety within four weeks of discontinuing the drug. Nevertheless, the optimal duration of treatment with anxiolytic drugs remains largely unstudied in all anxiety disorders and needs to be clarified.

Conclusions

It would be very useful to continue studies resulting in a better definition of anxiety disorders, with the help of clinical and paraclinical tools.

Firstly, a better knowledge of the clinical characteristics of anxiety disorders and perhaps a distinction between the different dimensions of anxiety trait versus state need be clarified. Research needs to regard the individualization of some new concepts such as anxiety depression syndrome and, more recently, 'double anxiety'. The usefulness of PD as a classification is now well established, but the clinical aspects highlighting this diagnosis could be better defined. Similarly for GAD, this type of work seems necessary along with clearly defined limits in the exploration of the syndrome.

Secondly, research also needs to focus on biological parameters; indeed, some new variables could be helpful in identifying the subtypes of anxiety. Particularly encouraging are pharmacological tests suggesting real differences between anxiety disorders in response to the same challenging agents[56]. For example, panic attacks were induced by intravenous sodium lactate in patients suffering from PD but not in patients suffering from OCD (Ref. 57), and a blunted growth hormone response to clonidine was found in PD (Ref. 58) but not in OCD (Ref. 59). Another interesting aspect of research in biological psychiatry concerns studies conducted in chronobiology. For example, we conducted a study that seems to show desynchronization of the circadian rhythm of temperature in OCD patients

compared with healthy subjects[60]. Even though this type of study needs to take many parameters into account, it is of a great importance in understanding anxiety disorders. For example, it would be helpful to distinguish the differences between physiological and pathological anxiety, especially in patients suffering from GAD or adjustment disorder.

Thirdly, neuroimaging studies, especially techniques to study brain function, have been greatly developed during the past few years, and they should contribute to our knowledge of the neuroanatomy and pathophysiology of anxiety disorders[61].

Lastly, the discovery of drugs able to contribute to a better understanding of the physiopathological mechanisms implicated in these disorders, is necessary; for example, the role of 5-HT antagonists in GAD, of CCK antagonists in PD, and of pentagastrin antagonists in SP should be studied.

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