

6. Treating anxiety

This chapter will answer the following questions:

- What is the most effective treatment for general anxiety disorder? (GAD)
- What is the most effective treatment for panic disorders? (PD)
- What is the most effective treatment for panic attacks?

The treatment of Generalized Anxiety Disorders (GAD) and Panic Disorder (PD) in Primary Care has the following objectives: relieve the symptoms, prevent the consequences and help and/or advise on the resolution of psycho-social problems, seeking effectiveness in terms of cost/benefit. An integrated focus must be applied, taking into account psychosocial, biological, and pharmacological measures.

6.1. Psychological treatment

Psychotherapy is a process of interpersonal communication between an expert professional (therapist) and a subject who needs help in regard to mental health problems (patient), the goal of which is to produce changes to improve the patient's mental health⁷¹, for the purpose of causing existing symptoms to disappear or change, attenuate or change behavior and promote growth and development of a positive personality⁷².

Qualitative study The published results of studies that ask people who visit Primary Care indicate that they either positively accept the psychological interventions²², or they prefer psychological therapy to pharmacological treatments as a way of treating mental health disorders⁷³.

A clinical research study done in Spain emphasized that the principles that must be included in a "support" relationship offered by the Primary Care doctor⁷⁴ and that are the core and the start of any therapeutic intervention. It is crucial that the clinical interview and adequate communication of the diagnosis and the etiological approach for the patient be suitable. The doctor-patient relationship can itself be considered an important therapeutic instrument⁷⁵.

When the professional, making use of the skill of the clinical interview, constructs a relationship based on active listening, he or she validates the patient's ideas and feelings, encourages the expression of emotions and from there comforts, dis-sents, informs, and reinforces independence.

Although the treatment is proposed from many different theoretical focuses, the following sections, within the different models of psychotherapeutic intervention for the treatment of anxiety disorders, describe the two main groups on which research has focused, mainly, its studies and within which brief and structured psychological interventions are being carried out in Primary Care.

Cognitive-behavioral therapies^{76,77}

This heading covers a set of techniques that incorporate elements of both Behavioral Therapy – which considers symptoms as a learning of maladapted patterns of behavior and its goal is to correct these patterns – and Cognitive Therapy, which takes into account affective and cognitive processes (expectations, beliefs, thoughts) whose distortion could be the cause of the symptoms, and whose purpose is the identification and analysis of those dysfunctional thoughts and beliefs and their relationship with the symptoms, and the construction of more adaptive and functional response techniques.

Cognitive-Behavioral Therapy (CBT) is an active and directive method in which the patient and therapist work jointly in a structured manner, with tasks outside of the session.

It uses both behavioral and cognitive techniques in different combinations depending on the symptoms to be counteracted: relaxation and breathing, autogenic training, cognitive restructuring, live and deferred exposure, thought-stopping, resolving problems, etc.

Psychodynamic psychotherapies⁷⁸

This heading covers an entire series of psychotherapies whose historic origins lie in Freud's research and psychoanalysis, and which have certain fundamental concepts in common, such as the conflict between the different aspects of the Ego, the existence of unconscious motivations in our behavior, the importance of early experiences, defense mechanisms as strategies to modulate psychic pain and anguish and the consideration of the therapeutic relationship as the promoting factor of the comprehension of the origin and continuation of the symptoms.

The goal of psychodynamic psychotherapies is to promote the comprehension and integration of the aspects of the Ego in conflict, finding new ways to integrate them to function and develop with greater freedom and effectiveness. Some of the techniques included in psychodynamic psychotherapies are brief psychotherapy and group psychotherapy.

In the most recent developments, psychodynamic psychotherapies have included aspects of cognitive and behavioral theories, which have led to the use of more directive intervention techniques, with precise delineation of the conflicts to be resolved. These include brief family psychotherapy, interpersonal therapy, and cognitive-analytical therapy.

In the study of anxiety disorders, interventions based on psychodynamic theories have been given little attention.

The guideline is mainly focused on CBT interventions. However, the distinction between the interventions included in treatments with CBT in the different studies covered here is difficult to make and different types of interventions are frequently combined within each CBT described.

6.1.1. Generalized Anxiety Disorder (GAD)

The psychological treatment of Generalized Anxiety Disorder (GAD) must apply techniques that allow patients to learn to control themselves gradually, keeping in mind that symptoms can be expected to increase in extreme situations. The idea is to give the subject resources that can be put into action as soon as an increase in anxiety symptoms is noted, without having to turn to medication automatically⁷⁹.

CPG (SR
and RCTS)
1++

The Clinical Practice Guidelines that were consulted while preparing this guideline^{70,80-82} consider Cognitive-Behavioral Therapy (CBT) to be the treatment of choice for GAD. In the Canadian guideline, the meta-analyses show that CBT reduces the symptoms of anxiety and is more effective for GAD than non-treatment or non-specific psychological treatment methods. The advantages of the therapy, in long-term studies, tend to persist from 6 months to 2 years after termination of the treatment⁸³⁻⁸⁵.

RCTS 1++

For the NICE, short-term CBT is as effective as pharmacological therapies, but comparative evidence is lacking to demonstrate long-term effectiveness. However, there is evidence that the majority of patients that have been tracked after treatment with CBT continue to enjoy the benefits of this treatment over the long term. Also, patient preferences must always be taken into account⁸⁰.

In the MOH guideline, of the patients treated with CBT, approximately 50% showed a clinically significant improvement, and maintained the improvement within a range of 6 to 12 months of monitoring⁸².

SR of RCTS
1++

A review from the Cochrane examines the efficacy and acceptability of psychological therapies categorized as cognitive-behavioral therapies (CBT), psychodynamic therapies, and support therapies, compared with normal treatment or with a patient on the waiting list for treatment, comparing them to each other, for patients with GAD⁸⁶. Each study identified the description of the normal type of treatment to ensure that treatment with active support treatments would not be included. The CBT interventions applied included: training for treatment of anxiety, cognitive restructuring, situational exposure, and desensitization through self-control. Relaxation training is also a key intervention in almost all of the studies on which the review was based. The general average duration of the treatment was eight months. The results were measured in two ways: 20% reduction in anxiety symptoms, as the definition of a clinically significant change in patients, or a reduction in symptoms measured using scales. Of the patients assigned to CBT, 46% showed a favorable clinical response after the treatment, significantly reducing the symptoms of anxiety, worry, and depression, in contrast to 14% in the groups of patients who were on the waiting list for treatment or with normal treatment.

Both individual and group intervention showed a similar effect after the treatment, but the patients assigned to individual psychological therapy were less likely to abandon the treatment than the patients assigned to group therapy. Older subjects also had a higher probability of abandoning the therapy⁸⁶.

The Cochrane review concluded that psychological therapy that uses a cognitive-behavioral focus is effective in treating GAD, but it ultimately demonstrates that there is no evidence on the effectiveness of psychological therapy to treat GAD over the long-term, for more than 12 months. There is no data available that demonstrates

the effectiveness of focuses other than CBT because there is insufficient evidence. More studies must be done to determine whether psychodynamic and support therapies are effective in treating GAD and whether CBT is more useful than them in treating this disorder⁸⁶.

SR of RCTS
1++ Another systematic review, based on two systematic reviews and seven later RCTSs also found that CBT (through a combination of interventions such as cognitive restructuring, exposure, relaxation, and systematic desensitization) compared with the control on the waiting list (no treatment) improved generalized anxiety after 4 to 12 weeks of treatment. In studies that compare the effectiveness of CBTs and relaxation techniques, practically all indicate the superiority of CBT.

RCTS 1++ There is a healthcare technology evaluation report that investigates the long-term results of treatment with CBT, in comparison with placebos, waiting list, pharmacological treatments (diazepam, fluvoxamine) and non-pharmacological treatments (Eye Movement Desensitization and Reprocessing (EMDR) and analytical psychotherapy)⁸⁸. The clinical tests were carried out within the scope of Primary Care and included anxiety disorders such as GAD. The average number of hours of therapy was 5.6, distributed over seven sessions. The cognitive-behavioral interventions included progressive muscular relaxation or relaxation, self-control of desensitization, gradual exposure or in vivo and in vitro exposure, cognitive restructuring, seeking alternative activities and enjoyable tasks and support through therapeutic counseling. Treatment with CBT was associated with better long-term results, in terms of overall gravity of symptoms, but not with respect to the change status of the diagnosis⁸⁹.

The report concludes that as a result of the chronic nature associated with anxiety disorders, failure to complete the treatment, and the quantity of intermediate treatments during the period monitored, the results obtained in the short term are not guaranteed over a longer period of time. Worse results were obtained in long-term treatment when patients presented more complex or serious GAD. No evidence was found to indicate that longer duration of CBT achieves longer-term effects, so the conclusion is that it is unlikely that clinics that go beyond the standard treatment protocols of approximately 10 sessions over a period of 6 months will achieve greater effectiveness⁸⁸.

The effectiveness of CBT has generated a need to develop accessible techniques for practice in Primary Care based on these principles. The RCTSs analyzed in preparing this guideline show different models, but the results are ultimately similar.

RCTS 1+ There are two RCTSs^{90,91} in which an integrated model in which family physicians are supported by specialists. The intervention lasts between four to eight sessions over 8 weeks, during which the patients are assisted in developing cognitive-behavioral skills that include: physical and cognitive relaxation strategies, recognition and analysis of thoughts that generate anxiety and lack of self-confidence, techniques to detect these thoughts, seeking useful alternatives and training in actions to resolve problems, techniques to improve sleep and work at home.

RCTS 1+ Other RCTSs⁹², in the context of PC, compare three interventions of increasing complexity: self-help with a manual – guided by the family physician – following the recommendations of clinical practice guidelines and referral to CBT in Specialized Care. Good results were obtained in all interventions, but the most fea-

sible and useful, according to the family physicians themselves, was guided self-help, consisting of five 20-minute sessions, in which the doctors explain anxiety and simple cognitive techniques, based on relaxation exercises and in vivo exposure, to identify anxiety-inducing thoughts and replace them with other more realistic and rational thoughts. Patients then work three hours per week at home. This allows family physicians to effectively treat patients that they do not feel need to be referred.

The effectiveness of CBT has also been demonstrated in experiences in our own context, with different studies done in healthcare centres to evaluate the effectiveness of group workshops on cognitive and relaxation techniques in reducing disorders such as GAD.

Pre-post-study-1

A pre-post-intervention study evaluated the effectiveness of group learning of controlled breathing and relaxation techniques and cognitive-behavioral techniques in 18 patient groups. The intervention is a workshop with 8 weekly sessions, lasting an hour and a half and including training in breathing control and psycho-relaxation, relaxation techniques (Jacobson and Schultz autogenic training) and cognitive techniques (dealing with stress, cognitive restructuring, assertiveness, problem-resolution techniques, self-esteem) using group dynamics. The professional who organizes and directs the workshops is a social worker. Ten-twelve people participate for 2 months, and using the Goldberg anxiety-depression scale (EADG) – 18 items, an average drop of post-intervention anxiety was demonstrated.

Non-randomized controlled study 1+

In another non-randomized controlled intervention in people with GAD and PD, the control group consisted of patients who received conventional treatment with anxiolytics and/or support therapy and the intervention group completed a course with 10 weekly sessions, given by a nurse, in which patients learned a relaxation exercise based on the Shultz autogenic method, and carried out group exercises on perception, communication, and handling stress and anxiety, among others. A qualitative evaluation was done at the end through discussion groups. The STAI (State Anxiety Inventory) test was used before and after the intervention in both groups. The conclusions drawn by the authors are that this type of intervention is effective to diminish temporary anxiety situations and to a lesser degree improves the normal tendency of a subject to react anxiously. Qualitatively, these groups improve self-esteem and the network of relations.

These experiences in our own setting^{93,94} coincide in that future research should advance the knowledge of the effect on non-pharmacological therapies in psychological disorders in Primary Care. The long-term effects must be measured, including a control group and blind procedures, evaluating the effect on the consumption of psycho-active drugs. All aimed at eliminating possible biases that may affect these studies.

Evidence on treatment with Cognitive-Behavioral Therapy (CBT) for Generalized Anxiety Disorder (GAD)

1 ++	CBT is effective in the treatment of GAD, since it decreases symptoms of anxiety, worry, and <i>depression</i> ^{70,80-82,86} .
1 ++	The CBT studied includes cognitive restructuring, exposure, relaxation and systematic desensitization, with an average of eight months of <i>treatment</i> ^{86,87} .
1 ++	There is no evidence to indicate that CBT applied for more than 6 months (10 sessions results in greater long-term effectiveness ⁸⁸ .
1 ++	CBT applied individually has a similar effect to group treatment, although individual therapy shows lower abandonment rates ⁸⁶ .
1 ++	Short-term CBT is as effective as pharmacological therapy, although there is no comparative evidence to demonstrate this effectiveness over the long term ⁸⁰ .
1 ++	Over the long term, the advantages of CBT lasted from 6 months to 2 years after completion of treatment ⁸³⁻⁸⁵ .
1 ++	The presentation of more complex or serious GAD initially, failure to complete the treatment, and the number of intermediate treatments during the period monitored are associated with worse long-term CBT results ⁸⁸ .
1 ++	There are insufficient studies that have evaluated the effectiveness of psychotherapeutic intervention techniques other than CBT for the treatment of GAD ⁸⁶ .
Application within the scope of Primary Care	
1. International	
There is evidence of the application of CBT and its effectiveness in PC through:	
1 +	An integrated model in which family physicians are supported by specialists over a period of 8 weeks (4-8 sessions) to help patients to develop cognitive-behavioral skills through relaxation, recognition of thoughts that generate anxiety and lack of self-confidence, seeking useful alternatives, and training in actions to resolve problems, techniques to improve sleep, and working at home ^{90,91} .
1 +	Using self-help with a manual, guided by the family physician: Five 20-minute sessions to explain anxiety, simple cognitive techniques (relaxation and in vivo exposure and identification of anxiety-inducing thoughts), with three hours of work at home per week ⁹² .
2. National	
1+ / 1-	In our context, group workshops, based on relaxation and simple cognitive techniques, given at healthcare centres by social workers and/or nursing staff (8 sessions, 1 per week) improve anxiety situations and self-esteem ^{93,94} .

Recommendations on Cognitive-Behavioral Therapy (CBT) for Generalized Anxiety Disorder (GAD)

General recommendations	
A	Cognitive-Behavioral Therapy (CBT) is recommended as one of the treatments of choice for Generalized Anxiety Disorder (GAD) due to its effectiveness at reducing the symptoms of anxiety, worry, and sadness, in both the short and long term, although patient preferences must be taken into consideration.
A	Actions with CBT must include a combination of measures such as cognitive restructuring, exposure, relaxation, and systematic desensitization.
A	CBT should be applied over the course of approximately 10 sessions (6 months) on average, as greater effectiveness is not achieved by applying the therapy for a longer time.
A	CBT can be applied individually or in a group, since the effects are similar, although individual treatment generates lower abandonment rates.
Primary Care	
B	The application of cognitive-behavioral actions (relaxation, recognition of anxiety-causing thoughts, and lack of self-confidence, seeking useful alternatives, and training in problem-solving techniques, techniques to improve sleep and work at home) by trained professionals in healthcare centres is recommended.
B	The organization of group workshops based on relaxation and applicable cognitive techniques in healthcare centres is recommended.
√	Group workshops should run for at least 8 sessions (1 per week), be structured and be directed by trained professionals from the Primary Attention teams.

6.1.2. Panic Disorder with or without agoraphobia (PD)

The essential characteristic of panic disorder (PD) is the presence of recurring serious anxiety attacks (panic attack). A distinction must be made between the symptomatic treatment of panic attacks and the treatment of the disorder as such. Panic attacks normally abate either spontaneously or with mediation, after 5 or 10 minutes. Treatment of panic disorder is a continuous treatment that is intended to suppress panic attacks and prevent relapses.

The main goal of psychological treatment of panic disorder (PD) is to consistently reduce the frequency, duration, and intensity of crises, with respect to the levels recorded before the diagnostic process and therapeutic treatment⁷⁹.

Meta-analysis 1+ The first reviews that were done demonstrated the effectiveness of different modes of psychotherapy for treating PD, comparing their effectiveness with respect to a short-term control treatment⁹⁵ or during follow-up⁹⁶; but they did show the need for an RCTS that will investigate the effects of long-term treatment and the effects of interruption of treatment.

SR of RCTS 1++ A systematic review evaluated the effectiveness of short-term psychodynamic psychotherapies for frequent mental disorders in relation to a minimal treatment, and with controls with no treatment. The results found for PD show moderate benefits that were maintained during short and medium-term monitoring; however the variability of the design of the study means that these conclusions are tentative and need to be confirmed with additional research.

SR of RCTS 1++ Results were also found that show other therapies, such as applied relaxation and client-centred therapy, to be therapies with probable beneficial effects for the treatment of PD⁹⁸.

However, most of the studies done thus far have focused more on evaluating the effectiveness of CBT.

CPG (SR and RCTS) 1+

In the guidelines from the NICE, the Canadian Psychiatric Association, and the MOH CBT is considered to be the treatment of choice for PD.

For the NICE, CBT, due to the existence of proof of a longer-lasting effect, is the recommended intervention for PD⁸⁰. However, patient preferences must be taken into account. CBT is effective with or without exposure, and for most patients, weekly sessions of 1 to 2 hours are recommended, until treatment is completed, at most 4 months after it starts.

Pre-post study 1-

According to the Canadian guideline, based on the meta-analyses studied, CBT is the most effective psychological treatment for PD. Also, there is cumulative evidence that shows that CBT may be more effective than medication in the prevention of relapse and that in long-term studies⁹⁹⁻¹⁰¹, the advantages of CBT were maintained for up to 2 years after treatment finished.⁷⁰

CPG (SR and RCTS) 1+

The MOH shows the evidence of the effectiveness of CBT that includes components such as psycho-education, exposure to symptoms or situations, cognitive restructuring, breathing techniques, and techniques to handle panic⁸².

Meta-analysis 1++

There is a meta-analysis¹⁰² that evaluates the effectiveness of CBT, comparing it with the control of non-treatment or the use of a placebo. Two-thirds of the studies included compare CBTs that include exposure techniques, with an average duration of 16 weeks. Questionnaires and scales were used to measure the results. The conclusion of the meta-analysis is that CBT, in addition to being effective in reducing PD, improves the quality of life of the patients and is associated with a reduction of depressive symptoms associated with the disorder. The limitations of the studies included in the meta-analysis are also specified, since the final results are always measured in terms of frequency of panic attacks, so it is suggested that future research also take the anticipatory anxiety state into account and include criteria of all aspects of the disorder (cognitive, behavioral, and arousal or activation state).

The aforementioned meta-analysis also evaluates the effectiveness of CBT and pharmacotherapy for PD, comparing the two treatments. Anti-depressants, especially tricyclics and serotonin reuptake inhibitors (SSRI), were used for the pharmacological treatment. The average duration of the treatment was around 12 to 13 weeks. According to the final results, both treatments are equally effective in improving anxiety symptoms, although depending on the type of analysis, effectiveness for CBT was slightly higher.

SR of RCTS 1+

The systematic review of Clinical Evidence analyzes the reviews and RCTSs on interventions whose goal is either to reduce the gravity or frequency of the panic attacks, or the phobic avoidance and anticipatory anxiety behavior, or to improve social and occupational functioning with minimum adverse effects generated by the treatment⁹⁸. To evaluate the effectiveness results, measurements were taken of the number of panic attacks, the intensity of agoraphobia, and the association of disability using specific and general scales, before and after treatment, and long term. This review concludes that CBT, in 20 sessions and lasting no more than 12-16 weeks, and using interventions such as relaxation, exposure procedures, and changing of

dysfunctional beliefs and negative automatic thoughts, compared with a pharmacological placebo, significantly increased the proportion of people with clinically and statistically significant improvement of panic symptoms in the six months of tracking.

Meta-analysis/SR
of RCTS 1+

A systematic review from the Swedish technology evaluation agency indicates that CBT that includes exposure relieves symptoms in PD without agoraphobia and with average or moderate agoraphobia. Its effectiveness for PD with serious agoraphobia was not established. In vivo exposure therapy as monotherapy relieves the symptoms of agoraphobic avoidance^{95,103}.

There are different primary studies that research the availability of protocols and resources to help PC physicians to put CBT-based interventions into practice specifically for PD.

A review article on the handling of PD in PC, in addition to highlighting the importance of communication skills in the evaluation of the disorder, psycho-education, and changes in lifestyle, proposes what is known as FPS (Focused Psychological Strategies) for CBT provided by family physicians, including: relaxation and breathing exercises, cognitive restructuring, and gradual exposure.

The variation of intervention models in PC is as broad as in the case of GAD.

RCTS 1+

Therapy is sometimes provided by psychologists, especially in healthcare systems in which they are integrated into PC. There is an **RCT**¹⁰⁵, for patients with PD and agoraphobia that compares three types of CBTs administered over the course of 12 weeks: standard (with eight 45-minute sessions), minimal contact (three 10-minute sessions and three 30-minute sessions), and bibliotherapy (three 11/2 hour sessions). Standard CBT was found to be most effective in terms of reducing the seriousness, altering symptoms, and social function, and was the treatment that, as it is shorter than other CBTs, represents an effective treatment for PD and agoraphobia in PC.

RCTS 1+

Another RCT in the context of PC, already mentioned in reference to the treatment of GAD, which compared self-help interventions guided by the family physician with a manual, following the recommendations in clinical practice guidelines, and referral to CBT in specialized care, also demonstrates that in patients with PD, the most feasible and beneficial intervention was guided self-help, which consisted of five 20-minute sessions, in which doctors explain anxiety and simple cognitive techniques (relaxation exercises and in vivo exposure) to identify anxiety-inducing thoughts and replace them with others. The therapy is supplemented by three hours of work at home per week, thus avoiding referrals to specialists⁹².

RCTS 1+

When the relative effectiveness of CBT was researched when applied individually and in groups by psychologists in the context of PC, no statistically significant differences were found between both treatments, but there was a clinically relevant difference in favor of individual therapy¹⁰⁶.

In Spain, some studies mention the need for close cooperation between Primary Care and Specialized Mental Health Care (MH) and continuous training program in MH for PC physicians was found to be important.

Pre-post study 1-,
Non-randomized
controlled study
1+

The studies done in our healthcare centres by social workers and/or nurses, already described for the treatment of GAD, also support the effectiveness of different cognitive workshops (handling stress, cognitive restructuring, techniques for problem-resolution) and group relaxation (Schultz autogenic method) in reducing anxiety in PD.

SR of different
types of studies
1+

The long-term effectiveness of CBT is still the objective of future research. The effectiveness of psychological therapy is compared with the effectiveness of pharmacological treatment, and the conclusions have determined not that CBT does not have lasting effects, but rather that more studies based on a robust methodology and carried out with reliable data are needed¹⁰⁷.

Evidence on Cognitive-Behavioral Therapy (CBT) for Panic Disorder (PD)

1 +	There is evidence that shows CBT as the best treatment for PD based on its longer-lasting effects ⁸⁰ .
1++	CBT significantly increases the proportion of people with clinically significant improvement of panic symptoms in a six-month follow-up, improved quality of life of the patient, and is associated with a reduction of depressive symptoms associated with the disorder. ^{98,102}
1 +	The CBT studied includes psycho-education, exposure to symptoms or situations, cognitive restructuring, breathing and relaxation techniques, and handling panic, with weekly sessions lasting 1 to 2 hours, over the course of 4 months of treatment ^{80,82} .
1 +	CBT that includes exposure relieves the symptoms of PD without agoraphobia or with average or moderate agoraphobia ⁹⁵ .
1 -	There is evidence that CBT may be effective in preventing relapse ⁹⁹⁻¹⁰¹ .
1 +	When the effectiveness of CBT and pharmacotherapy (SSRI and TADs) is compared, both treatments are equally effective in improving anxiety symptoms, although depending on the type of analysis, effectiveness was found to be slightly higher for CBT ¹⁰² .
1 +	Over the long term, the advantages of CBT lasted from 6 months to 2 years after completion of treatment ^{70,99-101} .
Application within the scope of Primary Care	
1. International	
There is evidence of the application of CBT and its effectiveness in PC for PD through:	
1 +	An integrated model in which family physicians are supported by psychologists. Patients receive a manual and for 12 weeks (8 sessions) CBT interventions are applied through exposure and cognitive restructuring, which are much more effective in reducing the gravity and altering symptoms and improving social functioning than minimal contact therapy (6 sessions) and bibliotherapy ¹⁰⁵ .
1 +	Self-help with a manual, under the guidance of the family physician. The family physicians hold five 20-minute sessions to explain anxiety, simple cognitive techniques (relaxation and <i>in vivo</i> exposure and identification of anxiety-inducing thoughts), with three hours of patient work at home per week ⁹² .
1 +	Between CBT applied individually and in groups, no statistically significant differences were found, but there was a clinically relevant difference in favor of individual therapy ¹⁰⁶ .
2. National	
1+ / 1-	In our context, group workshops, based on relaxation and simple cognitive techniques, given at healthcare centres by social workers and/or nursing staff (8 sessions, 1 per week) improve anxiety situations and self-esteem ^{93,94} .

Recommendations regarding Cognitive-Behavioral Therapy (CBT) for Panic Disorder (PD)

General recommendations	
A	Cognitive-Behavioral Therapy (CBT) is recommended as one of the treatments of choice for Panic Disorder (PD) because of its effectiveness in improving panic symptoms, quality of life, and reducing depression systems, although patient preferences must be taken into consideration.
A	CBT actions should include a combination of actions such as psycho-education, exposure to symptoms or situations, cognitive restructuring, techniques for relaxation, breathing, and handling panic.
A	CBT should be applied, on average, in 8-16 weekly sessions of 1 to 2 hours.
B	To relieve symptoms of PD with average or moderate agoraphobia, CBT actions are recommended, including <i>in vivo</i> exposure.
Primary Care	
B	The application of cognitive-behavioral actions is recommended for application in healthcare centres by trained professionals, preferably individually, through exposure and cognitive restructuring.
B	The organization of group workshops based on relaxation and applicable cognitive techniques in healthcare centres is recommended.
√	Group workshops should run for at least 8 sessions (1 per week), be structured and be directed by trained professionals from the Primary Attention teams.

6.1.3. Panic attack

Due to the high level of incapacitation perceived by patients who suffer panic attacks, this aspect has been considered to be an important part of the research.

In treating panic attacks, it is necessary to keep in mind that the episodes that characterize the disorder have a significant effect on the lives of the people who suffer it and that while they may occasionally improve, they do not normally disappear unless adequate treatment is received¹⁰⁸.

Some studies indicate that of people with panic attacks who go to a healthcare centre, 32% go to hospital emergency rooms, 26% to mental health facilities, and 35% to Primary Care. The family physician plays a very important role in the case of patients suffering from panic attacks. Patients who go to a healthcare centre with a panic attack are responding to the initial manifestations of their illness and present less serious symptoms than those who go to mental health services. This may partly explain why the results obtained with treatment in Primary Care are better in terms of lower frequency of visits and need for medication for this condition, as well as lower incidence of self-medication¹⁰⁹⁻¹¹².

CPG (Expert opinions) 4

Sufficient evidence was not found in trials researching symptomatic treatment of panic attacks, especially in terms of acute treatment of the crisis^{70,80-82}.

The Canadian guideline emphasizes the role of cognitive-behavioral therapy as an effective psychotherapeutic strategy for handling anxiety crises⁶¹. In our context, and within the scope of Primary Care, behavioral and support measures that contain psycho-education (calming the patient, written advice on actions), training in handling the symptoms (instruction in relaxation techniques and learning breathing exercises to handle hyperventilation), and exposure techniques could also be included. It is also important to inform the family regarding this type of actions in response to the appearance of a new crisis.

Evidence on Cognitive-Behavioral Therapy (CBT) for Panic Attack

4	Sufficient evidence was not found in trials researching symptomatic treatment of panic attacks, especially in terms of acute treatment of the crisis ^{70,80-82} .
4	The following techniques are recommended in PC to control symptoms related to panic attacks: <ul style="list-style-type: none"> • Behavioral and support measures the include psycho-education: calm the patient and advised actions in writing. • Training in the handling of symptoms: teaching of relaxation techniques and learning breathing exercises to handle hyperventilation. • Exposure techniques.
4	Information given to the family in regard to previous action can help if a new panic attack occurs.

Recommendations regarding Cognitive-Behavioral Therapy (CBT) in PC for Panic Attack

√	<p>The following psychological techniques are recommended in PC to control symptoms related to panic attacks:</p> <ul style="list-style-type: none"> • Behavioral and support measures the include psycho-education: calm the patient and advised actions in writing. • Training in the handling of symptoms: teaching of relaxation techniques and learning breathing exercises to handle hyperventilation. • Exposure techniques.
√	<p>The family should be informed regarding the type of actions to help in resolving any new attacks.</p>

6.2. Psychological techniques for Primary Care setting

Expert opinions 4 Independently from the focus from which one works, and whether the treatment is done individually or as a group, psychological interventions in PC must be done by trained professionals and must have common characteristics of applicability⁷⁷, which are the characteristics which differentiate them from the exercise of the support relationship that is created in Primary Care facilities:

- Structured: simple to learn and easy to apply.
- Brief and with specified times in the initial manualization.
- With specific objectives established after evaluation.
- Effectiveness described for the diagnosis to be treated.

6.2.1. Cognitive-behavioral techniques

Behavioral Techniques

The purpose of these techniques is to reduce symptoms by modifying the factors that reinforce the symptoms and/or gradual exposure to the anxiety-inducing stimuli. The table below describes these techniques:

Table 9*. Behavioral Techniques in Primary Care^{59,113}

Expert opinions 4	<p>Relaxation techniques: to achieve a state of hypoactivation that counteracts and helps control anxiety</p> <ul style="list-style-type: none">• Training in progressive relaxation• Training in breathing control <p>Exposure techniques: exposure to stimuli that cause anxiety, in order to predict and reduce adaptive responses</p> <ul style="list-style-type: none">• Systematic desensitization• Gradual exposure in vivo <p>Self-control techniques: these teach the patient the principles that govern the undesired behavior</p> <ul style="list-style-type: none">• Self-observation• Self-reinforcement or self-punishment• Control of stimuli <p>Training in social skills: after analyzing the problem behavior and retraining it.</p>
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*Modified García-Vera in Vázquez-Barquero⁶⁹.

Cognitive Techniques

Identify and analyze the dysfunctional thoughts and beliefs and their relationship with the symptoms, and construct more adaptive and functional response techniques.^{76,77}

Table 10. Cognitive Techniques^{113,114}

Expert opinions 4	<p>Self-instruction: detect the negative self-verbalization (“I won’t be able to”) and replace them with positive self-instruction (“I will be able to”) and prevent evasive responses to anticipatory anxiety.</p> <p>Training in the handling of anxiety symptoms: teaches the patient to use applied relaxation to control anxiety. The patient is trained to recognize the symptoms that reflect the presence of anxiety, in order to learn how to recognize the anxiety responses as they form, and to be able to use them as indicators to initiate the relaxation response.</p> <p>Cognitive distraction and thought stopping: focus attention on neutral, non-threatening stimuli (count streetlights, shoe store display windows, etc.).</p> <p>Problem-resolution techniques^{76,115,116}: in order to resolve stressful life situations in the most appropriate way. These techniques help to identify and define problems. They provide method for prioritizing objectives and specifying the steps to be carried out. This reduces the intensity of the apprehension, increases the feeling of control in response to negative circumstances, recognizing the milestones achieved, fosters initiative, and generates a more effective way of facing future problems.</p> <p>Cognitive restructuring^{58,59,76,77,117}: replaces irrational or distorted thoughts with other more rational ones. The work is structured around a skill-training model to help patients develop the ability to identify the disadaptive cognitions, comparing them with reality, and deactivating them by generating their own rational thoughts.</p>
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6.2.2. Psychodynamic orientation techniques

Psychodynamic Techniques

Expert
opinions 4

These techniques help to understand the symptoms and underlying conflicts (from the internal world or personal relations) through an empathic focus in which the therapist observes, comprehends, and receives the person's anxieties, and returns them so that they can be recognized and accepted by the patient, encouraging thinking and taking responsibility for themselves⁷⁸.

Table 11. Psychodynamic Techniques in Primary Care

Interpersonal Therapy (IPT)^{58,78,118}: frequent interpersonal aspects are identified: grieving, role transition, disputes, and interpersonal deficit. This is a manual-based intervention that is specifically designed for patients who present anxiety or depression symptoms in relation to stressful life events and who do not suffer from a serious mental disorder. The goal is to reduce stress and the symptoms, improving social functioning.

6.2.3. Other Techniques

Brief Family Therapy (BFT)¹¹⁹⁻¹²¹

Expert
opinions 4

This therapy understands the family as a set of elements that interact with each other and that cause people to persist in activities that keep the problems alive. The goal of the professional must be to stimulate to initiate a process of change. A proposal is formulated for actions that foster the desired changes to resolve the problem. The patient and the patient's family complete the process, without accompanying them to the end of the solution and without the entire family visiting the doctor.

Counseling Techniques (assisted counseling)^{59,117}

Use of relationships that develop self-awareness, emotional acceptance, growth, and personal resources. This may be directed to resolve specific problems, to make decisions, confronting a crisis, working through the feelings within conflicts, or improving relations with others. The problem is explored with the patient from effective comprehension to allow the patient to establish goals and objectives.

Most of these techniques, both cognitive-behavioral and psychodynamic, can be applied individually or in groups, provided that the intervention fulfills the requirements described earlier and is properly structured for application in a group format.

The most commonly used group therapies used in Primary Care for anxiety disorders are those called “Skill development”. They are used to apply the learning of breathing and relaxation techniques, facing and handling stress, resolving problems, and training and handling of anxiety, among others.

Evidence on psychological techniques applicable in Primary Care for Generalized Anxiety Disorder (GAD) and Panic Disorder (PD)

4	<p>The following common characteristics have been found in the brief interventions carried out in PC, individually or in groups, to obtain greater effectiveness⁷⁷:</p> <ul style="list-style-type: none"> • Done by trained professionals • Structured: simple to learn and easy to apply • Brief and with specified times in the initial manualization • With specific objectives established after evaluation • Effectiveness for the diagnosis to be treated should be described
4	<p>The following techniques are recommended in PC to reduce symptoms related to panic attacks:</p> <ul style="list-style-type: none"> • Relaxation techniques: training in progressive relaxation or breathing control • Exposure: systematic desensitization and gradual exposure in vivo • Self-control techniques: self-observation, self-reinforcement and self-punishment, and control of stimuli • Training in social skills: retraining problematic behaviors • Self-instruction: from negative self-verbalization to positive self-instruction • Training in the handling of anxiety symptoms: applied relaxation • Cognitive distraction and thought stopping: neutral, non-threatening stimuli • Problem-resolution techniques: identify and define problems • Cognitive restructuring: irrational or distorted thoughts replaced with other more rational ones • Interpersonal Therapy (IPT): identify interpersonal aspects • Brief family therapy (BFT): change process that understands the family as a set of elements that interact with each other. • <i>Counseling</i>: use of relations that develop self-awareness, emotional acceptance, growth, and personal resources.

Recommendations regarding psychological techniques applicable in Primary Care for Generalized Anxiety Disorder (GAD) and Panic Disorder (PD)

√	<p>Brief actions in PC should be carried out by trained professionals and should have a series of common characteristics of applicability: they should be structured, simple, easy to apply, short, with defined times, specific objectives, and described effectiveness.</p>
√	<p>The following are recommended as psychological techniques for possible application in PC to reduce anxiety symptoms associated with GAD and PD: techniques for relaxation, exposure, self-control, training in social skills, self-instruction, training in handling anxiety, cognitive distraction and thought stoppage, resolution of problems, cognitive restructuring, and interpersonal therapy.</p>

6.3. Pharmacological treatment

The goal of pharmacological treatment of anxiety disorders is to relieve the symptoms, prevent relapses, as well as the lasting effects, all with the best possible toleration of the medication.

6.3.1. Generalized Anxiety Disorder (GAD)

The chronic nature of the disorder must be taken into consideration when determining the therapeutic actions. Normally, prolonged treatments that can provide clinical stability are recommended.

Anti-depressants

SR of RCTS 1+ One of the first systematic reviews of RCTSs that use anti-depressants (imipramine, paroxetine, and trazodone) to treat anxiety disorders showed comparable effectiveness between benzodiazepines and anti-depressants for acute treatment of GAD¹²². The data gathered over the course of the last two decades has continued to highlight the effectiveness of anti-depressants in the treatment of GAD.

SR of RCTS 1++,
RCTS 1+ When the effectiveness of the anti-depressants imipramine, venlafaxine, and paroxetine and their degree of acceptance, measuring the results in terms of “absence of response” (the response defined as the absence of symptoms sufficient to fulfill the diagnostic criteria, with ratings of 1 or 2 – very significant improvement – in the Clinical Global Impressions – CGI), “abandonment rate”, and “specific side effects”, were studied against a placebo, it was observed that there is a greater probability of response to the treatment in the short term in the case of anti-depressants versus the placebo, with a global NNT for anti-depressants of 5.5 (CI of 95%:4.1;8.4), that there were no significant differences in terms of abandonment between the two, and that the side effects manifested themselves most frequently in the groups treated with drugs versus those treated with the placebo. The fact that the abandonment rates did not show significant differences between the groups treated with anti-depressants and those treated with the placebo suggests that patients with GAD can tolerate the use of these drugs well. When tricyclic anti-depressants are compared with new anti-depressants, the results in terms of effectiveness and tolerability are similar for paroxetine and imipramine. Although venlafaxine and paroxetine are associated with a better level of acceptance, no differences were found with tricyclic imipramine in terms of abandonment, which is possibly a more solid indicator of the level of acceptance^{123,124}.

SR of RCTS 1++,
RCTS 1+ Another systematic review and later trials expanded the evaluation of the aforementioned anti-depressants with sertraline, escitalopram, and opipramol*, comparing them with a placebo. It was observed that these drugs increase response rates and improve symptoms of GAD.^{87,125} Research with other anti-depressants for treating GAD highlight the role of other drugs, such as duloxetine, for its good tolerance levels and effectiveness in comparison with a placebo to reduce functional alterations of patients and improve quality of life and well-being. More studies are needed on its effectiveness in comparison with other anti-depressants¹²⁶⁻¹²⁸.

SR of RCTS 1+,,
Series of cases 3 The adverse effects found for the aforementioned families of anti-depressants are associated with sedation, dizziness, nausea, dry mouth, constipation, falls, and sexual dysfunction, among others, although many of the trials does not reflect their statistical significance. However, there is evidence that demonstrates that most of them (with the exception of dizziness and sexual dysfunction) decrease after 6 months in patients who continued with the medication. On the other hand, the sudden interruption of treatment with SSRIs is associated with adverse effects such as dizziness, headache, nausea, vomiting, diarrhea, movement disorders, insomnia, irritability, visual alterations, lethargy, anorexia, and states of despondency. The possible increase in the risk of self-inflicted injuries, suicide, and hyponatremia must be taken into consideration in regard to the use of SSRIs.

SR of RCTS 1+,,
Series of cases 3,
SR of different
types of studies/
Cohort
studies 2+,,
Meta-analysis 1+ The US FDA (Food and Drug Administration) has warned of complications when taken during pregnancy: congenital malformations, especially cardiac malformations, if paroxetine is used in the first trimester of pregnancy, increasing its pregnancy risk category from C to D (the FDA's classification for medications based on their teratogenic potential)^{87,130}. Also, when SSRIs are taken in the final phases of pregnancy, there is some evidence that indicates that these drugs interfere with the respiratory and parasympathetic systems of neonatal infants, along with increased risk of respiratory and central nervous system symptoms. Hypoglycemia and neonatal adaptation problems may also be encountered. However, all of these results are not always due to the toxicity or removal of SSRIs. To reduce the potential risk of adverse neonatal effects, the lowest effective dose of SSRIs should be used with the shortest possible treatment duration, as monotherapy whenever feasible. During pregnancy, the choice of the treatment must consider whether the potential advantages for the mother of the prescribed SSRIs outweigh the possible risks to the fetus¹³¹⁻¹³⁶.

* Opipramol: anti-depressant not marketed in Spain.

CPG (SR and RCTS) 1++, RCTS 1++, RCTS 1+

The guidelines from the NICE, Canadian Psychiatric Association, and MOH^{70,80-82}, consider the use of anti-depressants to be one of the treatments of choice for GAD. The Canadian guideline specified paroxetine, escitalopram, sertraline, and slow-release venlafaxine as the best options for pharmacological treatment because of their significant improvements in quality of life and the symptoms related to functional disability^{70,137}. Paroxetine, escitalopram, and venlafaxine have demonstrated long-term effectiveness, with response rates that continue to increase beyond 6 months of treatment. For patients who interrupt treatment, there is a risk of relapse from 20% to 40% between 6 and 12 months after treatment is interrupted. This therefore suggests that long-term treatment will often be necessary^{70,138-140}.

CPG (Series of cases) 3, CPG (Expert opinions) 4

Warning regarding venlafaxine: the NICE guideline indicates that this drug has a higher probability of interruption of treatment due to side effects and higher cost than SSRIs, compared with the same level of effectiveness. *It also includes a warning based on evidence provided by the MHRA (Medicines and Healthcare products Regulatory Agency).* This agency has warned against the cardio-toxic and hypertensive effects of this drug, especially associated with higher-than-therapeutic dosages (a dosage not exceeding 75 mg/day is recommended). NICE recommends that when venlafaxine is prescribed to patients with hypertension, that the hypertension be controlled and that it not be prescribed to patients with a high risk of cardiac arrhythmia or recent heart attack^{81,141}.

When the response to the optimal dosage of one of the SSRIs is inadequate or if SSRIs are not well tolerated, the patient should switch to another SSRI. If there is no improvement after 8-12 weeks, consider using another drug with a different mechanism of action (NSRI, TAD)^{70,80}.

Evidence regarding anti-depressants for Generalized Anxiety Disorder (GAD)

1++ , 1 +	The anti-depressants imipramine, venlafaxine, paroxetine, sertraline, escitalopram, duloxetine and opipramol have been demonstrated to be effective with GAD ^{87,123-125} .
1++	The anti-depressants imipramine, venlafaxine, and paroxetine, present the following with respect to a placebo ^{123,124} : - Increased probability of response to the treatment in the short term. - More frequent side effects, although significant differences were not observed in terms of the abandonment rate.
1++	Paroxetine and imipramine showed similar tolerability and effectiveness ¹²³ .
1++	No differences were found among imipramine, venlafaxine, and paroxetine in terms of abandonment ^{123,124} .
1++ , 1 +	Sertraline, escitalopram, duloxetine, and opipramol are effective at increasing response rates and improving symptoms in comparison with a placebo ^{87,125} .
1++	The adverse effects of anti-depressants described include sedation. ⁸⁷ dizziness, nausea, dry mouth, constipation, falls, and sexual dysfunction (with the exception of dizziness and sexual dysfunction) decrease after 6 months in patients who continue with the medication ⁸⁷ .
3	The FDA has given several warnings in relation to the use of SSRIs and increased risk of: self-inflicted injuries and suicide, hyponatremia and complications when taken during pregnancy (congenital malformations with paroxetine in early stages of pregnancy) ^{87,130} .
1 + 2++	Also, when SSRIs are taken in the final phases of pregnancy, there is some evidence that indicates that these drugs interfere with the respiratory and parasympathetic systems of neonatal infants, along with increased risk of respiratory and central nervous system symptoms. Hypoglycemia and neonatal adaptation problems may also be encountered. However, all of these results are not always due to the toxicity or removal of SSRIs ¹³¹⁻¹³⁶ .
1++	On the other hand, the sudden interruption of treatment with SSRIs is associated with adverse effects such as dizziness, headache, nausea, vomiting, diarrhea, movement disorders, insomnia, irritability, visual alterations, lethargy, anorexia, and states of despondency.
1++	Paroxetine, escitalopram, and venlafaxine are effective over the long term, with response rates that continue to increase after 6 months of treatment ^{70,138-140} .
1 +	Interruption of treatment poses a risk of relapse of 20% to 40% between 6 and 12 after the interruption of treatment ^{70,138-140} .
3	The MHRA (Medicines and Healthcare products Regulatory Agency) has warned of the cardio-toxic and hypertensive effects of venlafaxine, especially associated higher-than-therapeutic doses ^{81,141} .

Recommendations regarding anti-depressants for Generalized Anxiety Disorder (GAD)

A	The use of anti-depressants is recommended as one of the pharmacological treatments of choice for GAD.
B	The anti-depressants recommended for use are SSRIs (paroxetine, sertraline, or escitalopram), SNSRIs (slow-release venlafaxine) y and TADs (imipramine).
C	The prescription of venlafaxine is not recommended to patients at high risk of cardiac arrhythmia or recent myocardial infarct, and will only be used in patients with hypertension when the hypertension is controlled.
√	When the response to the optimal dosage of one of the SSRIs is inadequate or if they are not well tolerated, the patient should switch to another SSRI. If there is no improvement after 8-12 weeks, consider using another drug with a different mechanism of action (SNSRI, TAD).
B	During pregnancy, the choice of the treatment must consider whether the potential advantages for the mother of the prescribed SSRIs outweigh the possible risks to the embryo.
B	To reduce the potential risk of adverse neonatal effects, the lowest effective dose of SSRIs should be used with the shortest possible treatment duration, as monotherapy.
√	In prescribing anti-depressants, patients should be informed of the therapeutic objectives, the duration of the treatment, possible side effects, and the risks of sudden interruption of the treatment.
√	The following must be taken into account when prescribing anti-depressants: age, previous treatments, tolerance, possibility of pregnancy, side effects, patient preferences, and cost as well as effectiveness.

Note: The Technical Dossier from the Spanish Agency for Medications and Healthcare Products (AEMPS)¹⁴² for sertraline does not include the therapeutic indication for GAD. In the case of imipramine (Technical Dossier unavailable), the prospectus does not include this indication either.

Anxiolytics: benzodiazepines (BDZs)

BDZs are agents that depress the nervous system and they have general effect against anxiety, since they promote physical and mental relaxation, reducing nervous activity in the brain (gabaergic action).

CPG (SR and RCTS) 1++,1+

BDZs are part of a family of drugs that have demonstrated their effectiveness in the treatment of generalized anxiety^{70,80-82}.

Alprazolam, bromazepam, lorazepam, and diazepam have been proven to be effective in the treatment of GAD, and the Canadian guideline includes them as the second-tier pharmacological treatment. There is insufficient evidence evaluating the effectiveness of clonazepam, with long average life and low potential for rebound anxiety, but it is probable that benefits similar to those of other BDZs will be obtained⁷⁰.

CPG (SR and RCTS) 1+

BDZs provide fast initial relief of anxiety symptoms, but the evidence suggests that their effects do not differ significantly from those obtained with a placebo after 4 to 6 weeks of treatment. Also, BDZs primarily reduce somatic symptoms more than psychic symptoms (apprehension), which are the symptoms that define GAD⁷⁰.

SR of different types of studies 2++, SR of different types of studies 2++, Observational study 2+, Meta-analysis 1++, SR of different types of studies 2++/
Observational studies 2+, CPG (SR and RCTS) 1+

Side effects have been observed with the use of benzodiazepines in terms of increased risk of dependency, tolerance, sedation, traffic accidents, and effects of suspension of treatment (rebound anxiety)⁸⁷. Existing evidence is insufficient to determine whether during pregnancy, the potential benefits of BDZs for the mother outweigh the possible risks to the fetus¹⁴²⁻¹⁴⁴. To avoid the potential risk of congenital defects, the lowest effective dosage of BDZs should be used, with the shortest possible treatment duration, and as monotherapy. If higher concentrations are required, the daily dosage should be divided into two or three doses, always avoiding use during the first trimester^{143,145}. In advanced stages of pregnancy or during nursing, BDZs can cause adverse effects in neonatal infants (neonatal hypotonia, withdrawal syndrome, sedation, and hypothermia)^{82,87,146-149}.

Due to its effectiveness and the adverse effects described, short-term use is recommended, not extending beyond 2 to 4 weeks, especially when rapid control of the symptoms is required and while waiting for response to the benefits of treatment with anti-depressants or CBT. Long-term use must be closely supervised^{70,80-82}.

Evidence on benzodiazepines (BDZ) for Generalized Anxiety Disorder (GAD)

1++	Alprazolam, bromazepam, lorazepam, and diazepam have been proven to be effective in the treatment of GAD ⁷⁰ .
1 +	There is insufficient evidence evaluating the effectiveness of clonazepam, with long average life and low potential for rebound anxiety, but it is probable that benefits similar to those of other BDZs will be obtained ⁷⁰ .
1 +	BDZs provide fast initial relief of anxiety symptoms, but the evidence suggests that their effects do not differ significantly from those obtained with a placebo after 4 to 6 weeks of treatment.
1 +	Also, BDZs primarily reduce somatic symptoms more than psychic symptoms (apprehension), which are the symptoms that define GAD ⁷⁰ .
2++	The use of BDZs is associated with higher risk of dependence, tolerance, sedation, traffic accidents, and withdrawal effects (rebound anxiety) ⁸⁷ .
2++ 2+	Existing evidence is insufficient to determine whether during pregnancy, the potential benefits of BDZs for the mother outweigh the possible risks to the fetus ¹⁴²⁻¹⁴⁴ .
2++ 2+	There are adverse effects for neonatal infants when prescribed in advanced stages of pregnancy or during nursing (neonatal hypotonia, withdrawal syndrome, sedation, and hypothermia) ^{82,87,146-149} .

Recommendations regarding benzodiazepines (BDZ) for Generalized Anxiety Disorder (GAD)

B	The short-term use of BDZs not longer than 4 weeks is recommended when rapid control of symptoms is not crucial or while waiting for the response to treatment with anti-depressants or CBT.
B	Alprazolam, bromazepam, lorazepam, and diazepam are the BDZs recommended for use.
B	To avoid the potential risk of congenital defects, the lowest effective dosage of BDZs should be used, with the shortest possible treatment duration, and as monotherapy. If higher concentrations are required, the daily dosage should be divided into two or three doses, always avoiding use during the first trimester.
√	When prescribing BDZs, patients should be informed of the therapeutic objectives, the duration of the treatment, and the possible side effects.
√	The following should be taken into consideration when prescribing BDZs: age, previous treatments, tolerability, possibility of pregnancy, side effects, patient preferences, and cost as well as effectiveness.

Other drugs

Other drugs considered in the treatment of GAD are:

Azapirones

CPG (SR and RCTS) 1+, SR of RCTS 1++, Meta-analysis 1++

Azapirones are a family of anxiolytic drugs that act on the 5-HT_{1A} receptor. The effectiveness and acceptability of azapirones (buspirone) compared with a placebo or other treatments has been evaluated, and they appear to be useful and better than the placebo over the short term (four to nine weeks) in treating GAD, especially if patients have not taken benzodiazepines before. It is not possible to conclude whether azapirones are better than benzodiazepines, anti-depressants, psychotherapy, hydroxycine, or the extract from the kava kava plant. The side effects do not appear to be serious and they involve physical symptoms (nausea, dizziness, and drowsiness) above all^{70,145,150}.

Since GAD is generally chronic in nature, more studies must be done to establish conclusions regarding its long-term effectiveness.

Although azapirones have been approved for treatment of GAD in Spain, their use is very limited.

Pregabalin

CPG (SR and RCTS) 1+ RCTS 1+

Pregabalin is an anti-convulsive that when compared with a placebo, has been proven effective against the psychic and somatic symptoms of GAD, and is also tolerated by the majority of patients. The adverse effects associated with it include drowsiness, vertigo, and headache. Clinical experience with this drug is limited^{70,87,151-154}.

Hydroxicine

CPG (SR and RCTS) 1+, SR of RCTS 1+

Hydroxicine is a medication derived from piperidine, used generally as an anti-histamine. It also acts as a sedative and tranquilizer, which makes it useful for treating anxiety.

When hydroxicine was compared with a placebo, it was found to improve anxiety symptoms. When compared with other drugs, such as bromazepam and buspirone, no significant differences in effectiveness were observed. The side effects found are, above all, headache and drowsiness. Clinical experience with this drug is also limited^{70,87}.

Atypical anti-psychotics

CPG (RCTS) 1-, RCTS 1-

Open trials with small sample sizes suggest that the atypical anti-psychotics olanzapine, risperidone, and ziprasidone can have some benefit as adjuvant drugs in the treatment of refractory GAD, although controlled trials with placebos, randomized double-blind studies, and greater strength are required to verify its effectiveness and safety^{70,155,156}.

Other

CPG (RCTS) 1+, RCTS 1+/1-

Other anti-depressants such as mirtazapine, zitalopram, trazodone, and slow-release bupropion, anti-convulsives such as tiagabine, the drug used in treating Lateral Amyotrophic Sclerosis (ryluzol), and new anxiolytics like deramcyclane may show some effectiveness in treating GAD^{70,157-159}.

RCTS with placebos and larger sample sizes are needed to confirm these results.

Not recommended

CPG (RCTS) 1+

Beta-blockers such as propranolol have not been found to be more effective than placebos in treating GAD^{70,80}.

Evidence on other drugs for Generalized Anxiety Disorder (GAD)

Azapirones	
1 + 1 ++	Azapirones (buspirone) appear to be effective in controlling the symptoms of GAD over the short term (4 to 9 weeks), especially if the patients have not taken BDZs before ^{70,145,150} .
1 + 1 ++	It is not possible to conclude whether azapirones are better than benzodiazepines, anti-depressants, psychotherapy, hydroxicine, or the extract from the kava kava plant ^{70,145,150} .
1 + 1 ++	The side effects described do not appear to be serious and they involve physical symptoms (nausea, dizziness, and drowsiness) above all ^{70,145,150} .
Pregabalin	
1 +	Has been shown to be effective against the psychic and somatic symptoms of GAD and is also tolerated by most patients ^{70,87,151-154} .
1 +	The adverse effects include drowsiness, vertigo, and headache ^{70,87,151-154} .
Hydroxicine	
1 +	Improves anxiety symptoms when compared with a placebo, although differences in effectiveness were not observed when compared with bromazepam and buspirone ^{70,87} .
1 +	The side effects found include headache and drowsiness ^{70,87} .
Atypical anti-psychotics	
1-	Olanzapine, risperidone, and ziprasidone can have some benefit as adjuvant drugs in the treatment of refractory GAD, although controlled trials with placebos, randomized double-blind studies, and greater strength are required to verify its effectiveness and safety ^{70,155-156} .
Other	
1+, 1-	Other anti-depressants such as mirtazapine, zitalopram, trazodone, and slow-release bupropion, anti-convulsives such as tiagabine, the drug used in treating Lateral Amyotrophic Sclerosis (ryluzol), and new anxiolytics like deramcyclane may show some effectiveness in treating GAD ^{70,157-159} .
Not recommended	
1 +	Beta-blockers (propranolol) have not been found to be more effective than placebos in treating GAD ^{70,80} .

Recommendations regarding other drugs for Generalized Anxiety Disorder (GAD)

Other drugs	
B	Azapirones (buspirone) can be used short term, especially in patients with GAD who have not previously taken BDZs, although their use is very limited in Spain.
√	The use of other drugs such as pregabalin, hydroxicine, atypical anti-psychotics, and others, either due to their limited clinical experience or indication for refractory GAD, should be prescribed after the patient has been evaluated in a Centre specializing in Mental Health.
Not recommended	
B	The use of Beta-blockers (propranolol) is not recommended to treat GAD.

6.3.2. Panic Disorder with or without agoraphobia (PD)

The basic goal of pharmacological treatment of panic disorder is to block the appearance of new panic attacks. As a secondary effect, this also provokes other beneficial actions in patients, relieving anticipatory anxiety, improving self-confidence, and phobic avoidance, with a positive effect on associated depression and improved overall functioning^{160,161}.

As with generalized anxiety disorder, panic disorder is also characterized by a high tendency to become chronic and is also associated with frequent complications¹⁶². Specific control is therefore advisable with prolonged treatments to ensure clinical maintenance.

Anti-depressants

Meta-analysis 1+ One of the first meta-analyses with RCTS that used anti-depressants to treat PD demonstrated the effectiveness of SSRIs for this disorder¹⁶³.

SR of RCTS 1+ Along this same line, later reviews that analyzed the effectiveness of anti-depressants found that paroxetine, fluoxetine, fluvoxamine, citalopram, sertraline, chlorimipramine, and imipramine improved the symptoms of PD in comparison with a placebo. The adverse affects associated with these drugs are headache, trembling, dry mouth, drowsiness, nausea, and dizziness, among others. The percentage of abandonment due to adverse effects was 11% and was similar among the SSRIs and TADs^{98,164}.

Series of cases 3, SR of different types of studies/ Cohort studies 2++, Meta-analysis 1+ TheUSFDA(FoodandDrugAdministration)hasissuedseveralwarningsinregardto the use of SSRIs and increased risk of self-inflicted injury, suicide, and hyponatremia¹²⁹. It has also warned of complications when taken during pregnancy: persistent neonatal pulmonary hypertension and congenital malformations, especially cardiac malformations, if paroxetine is used in the first trimester of pregnancy, increasing its pregnancy risk category from C to D (the FDA's classification for medications based on their teratogenic potential)¹³⁰. Also, when SSRIs are taken in the final phases of pregnancy, there is some evidence that indicates that these drugs interfere with the respiratory and parasympathetic systems of neonatal infants, along with increased risk of respiratory and central nervous system symptoms. Effects of hypoglycemia and adaptation problems may also be observed. However, all of these results are not always due to the toxicity or removal of SSRIs. To prevent potential risk of adverse neonatal effects, the lowest effective dose of SSRIs should be used with the shortest possible treatment duration, with the possibility of use as monotherapy¹³¹⁻¹³⁶.

CPG (SR and RCTS) 1++ The guidelines from the NICE, Canadian Psychiatric Association, and MOH consider the use of SSRI anti-depressants to be the pharmacological treatment of choice for PD^{70,80-82}.

CPG (SR and RCTS) 1+, RCTS 1+	The Canadian guideline specifies citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and slow-release venlafaxine as the best choices for pharmacological treatment due to their significant improvement in the gravity of the panic. The aforementioned SSRIs also show a significant improvement in anticipatory anxiety and in agoraphobic avoidance, as well as in the symptoms related to functional disability and quality of life. Paroxetine, citalopram, fluoxetine, sertraline, and venlafaxine have demonstrated prolonged benefits and continued improvements over the course of 6 to 12 months of treatment ^{70,165,166} .
Series of cases 3	In terms of the use of venlafaxine, the MHRA (Medicines and Healthcare products Regulatory Agency) has warned of the cardio-toxic and hypertensive effects of venlafaxine, especially associated higher-than-therapeutic doses ¹⁴¹ .
SR of different types of studies 2++, CPG (SR and RCTS) 1+, RCTS 1+	There is limited evidence in regard to long-term persistence (longer than 6 months after treatment has been completed) of the benefits obtained with short-term treatments when the continuation of the treatment is not maintained ¹⁶⁷ and it is difficult to establish the ideal duration of pharmacological treatment for PD. Although imipramine and venlafaxine have been proven to prevent long-term relapse in comparison with the placebo, the interruption of treatment with anti-depressants poses a risk of relapse, so therapy in many patients should be applied long-term (at least 12 months) ^{70,168} .
	The treatments administered during the studies and their follow-up period must be better supervised in order to obtain more data on the long-term results.
CPG (RCTS) 1+, RCTS 1-	Research with other anti-depressants in the treatment of PD have demonstrated the effectiveness of mirtazapine and milnacipran (anti-depressant serotonin-5HT and noradrenalin-NA reuptake inhibitor) in open trials ^{70,169} .
CPG (RCTS) 1+	Other studies with MAOIs and MARIs show that some, such as fenelzine, appear to be effective in the treatment of PD. Trials on the effectiveness of MARI (moclobemide) do not show such clear results. Due to the potentially serious side effects and interactions with other drugs and dietary components, its use is recommended only when other drugs have failed ^{70,82} .
CPG (expert opinions) 4	When the response to the optimal dosage of one of the SSRIs is inadequate or if they are not well tolerated, the patient should switch to another SSRI. If there is no improvement after 8-12 weeks, consider using another drug with a different mechanism of action (NSRI, TAD, mirtazapine) ^{70,80} .

Evidence on anti-depressants for Panic Disorder (PD)

1 +	Paroxetine, fluoxetine, fluvoxamine, citalopram, sertraline, chlorimipramine, and imipramine, improve the symptoms of PD in comparison with a placebo ^{98,164} .
1 +	The adverse effects of the described anti-depressants include headache, trembling, dry mouth, drowsiness, nausea, and dizziness, among others ^{98,164} .
1 +	The percentage of treatment abandonment due to these adverse effects was 11% and was similar among the SSRIs and TADs ^{98,164} .
3	The FDA has given several warnings in relation to the use of SSRIs and increased risk of: self-inflicted injuries and suicide, hyponatremia and complications when taken during pregnancy (persistent neonatal pulmonary hypertension and congenital malformations with paroxetine in early stages of pregnancy) ^{129,130} .
1 + 2++	Also, when SSRIs are taken in the final phases of pregnancy, there is some evidence that indicates that these drugs interfere with the respiratory and parasympathetic systems of neonatal infants, along with increased risk of respiratory and central nervous system symptoms. Hypoglycemia and neonatal adaptation problems may also be encountered. However, all of these results are not always due to the toxicity or removal of SSRIs ¹³¹⁻¹³⁶ .
1 +	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and slow-release venlafaxine significantly improve the severity of panic ^{70,165,166} .
1 +	These SSRIs also show a significant improvement in anticipatory anxiety and in agoraphobic avoidance, as well as in the symptoms related to functional disability and quality of life ^{70,165,166} .
3	The MHRA (Medicines and Healthcare products Regulatory Agency) has warned of the cardio-toxic and hypertensive effects of venlafaxine, especially associated higher-than-therapeutic doses ¹⁴¹ .
1 +	Paroxetine, citalopram, fluoxetine, sertraline, and venlafaxine have demonstrated prolonged benefits over the course of 6 to 12 months of treatment ^{70,165,166} .
2++	There is limited evidence on the long-term persistence (more than 6 months after completion of treatment) of the benefits obtained with short-term treatments when the treatments are not continued ¹⁶⁷ .
1 + 1-	Mirtazapine and milnacipran (serotonin-5HT and noradrenalin-NA reuptake inhibitors) have proven effective in open trials ^{70,169} .
1 +	Some MAOIs such as fenzelzine appear to be effective in the treatment of PD. Trials on the effectiveness of MARI (moclobemide) have not shown such clear results ^{70,82} .

Recommendations regarding anti-depressants for Panic Disorder (PD)

A	The use of anti-depressants is recommended as one of the pharmacological treatments of choice for PD.
B	In terms of anti-depressants recommended for use, SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNSRIs (slow-release venlafaxine) and TADs (chlorimipramine, imipramine).
C	The prescription of venlafaxine is not recommended to patients at high risk of cardiac arrhythmia or recent myocardial infarct, and will only be used in patients with hypertension when the hypertension is controlled.
√	When the response to the optimal dosage of one of the SSRIs is inadequate or if they are not well tolerated, the patient should switch to another SSRI. If there is no improvement after 8-12 weeks, consider using another drug with a different mechanism of action (NSRI, TAD, mirtazapine).
B	The interruption of treatment with anti-depressants poses a risk of relapse, so therapy in many patients should be applied long-term (at least 12 months).
B	During pregnancy, the choice of the treatment must consider whether the potential advantages for the mother of the prescribed SSRIs outweigh the possible risks to the embryo.
B	To prevent potential risk of adverse neonatal effects, the lowest effective dose of SSRIs should be used with the shortest possible treatment duration, with the possibility of use as monotherapy.
√	In prescribing anti-depressants, patients should be informed of the therapeutic objectives, the duration of the treatment, possible side effects, and the risks of sudden interruption of the treatment.
√	The following must be taken into account when prescribing anti-depressants: age, previous treatments, tolerance, possibility of pregnancy, side effects, patient preferences, and cost as well as effectiveness.

Note¹⁴²:

- The Technical Dossier from the Spanish Agency for Medications and Healthcare Products (AEMPS) for venlafaxine, fluoxetine, and fluvoxamine does not include the therapeutic indication for PD.
- The Technical Dossier for chlorimipramine and the prospectus of imipramine (Technical Dossier not available) includes indication for panic attacks, but not panic disorder.

Anxiolytics - benzodiazepines (BDZ)

Benzodiazepines form part of a family of drugs that have proven their effectiveness in treating PD^{70,80-82}.

CPG (SR and RCTS) 1++, SR of RCTS 1++, RCTS 1+, RCTS 1-, CPG (RCTS 1+, CPG (RCTS) 1+, SR of RCTS 1+, RCTS 1+

Alprazolam, clonazepam, lorazepam, and diazepam have been proven to be effective in the treatment of PD, and the Canadian guideline includes them as the second-tier pharmacological treatment^{70,98}. Alprazolam has been proven to reduce the frequency of panic attacks and symptoms of agoraphobia and anticipatory anxiety¹⁶⁶. The slow-release formula appears to have good initial speed of effect, with the advantage of longer duration of its therapeutic action¹⁷⁰. The short-term use of clonazepam at the start of treatment, along with SSRIs can result in faster response⁶¹. However, BDZs are associated with a wide spectrum of adverse effects both during and after treatment (dependence, withdrawal syndrome when stopped, and recurrence if treatment is discontinued). This effect of sudden withdrawal has been observed in patients with PD with alprazolam^{82,98,171}.

CPG (SR and RCTS) 1+

Since the long-term use of BDZs is associated with problems, their use is recommended for a limited time (short term), with the lowest possible dosage to reduce symptoms of PD, with the dosage reduced gradually. Short-term use is also recommended at any time to reduce agitation or acute or serious anxiety. The selected guidelines do not recommend long-term use, but if used, they add that usage must be supervised^{70,80-82}.

SR of different types of studies 2+/
Observational studies 2+

Existing evidence is insufficient to determine whether during pregnancy, the potential benefits of BDZs for the mother outweigh the possible risks to the fetus¹⁴²⁻¹⁴⁴. To avoid the potential risk of congenital defects, the lowest effective dosage of BDZs should be used, with the shortest possible treatment duration, and as monotherapy. If higher concentrations are required, the daily dosage should be divided into two or three doses, always avoiding use during the first trimester¹⁴³. In advanced stages of pregnancy or during nursing, BDZs can cause adverse effects in neonatal infants (neonatal hypotonia, withdrawal syndrome, sedation, and hypothermia).^{82,87,146-149}

Evidence on benzodiazepines for Panic Disorder (PD)

1++	Alprazolam, clonazepam, lorazepam, and diazepam have been proven to be effective in the treatment of GAD ^{70,98} .
1 + 1-	Alprazolam has been proven to reduce panic attacks and symptoms of agoraphobia and anticipatory anxiety. Its slow-release formula has the same initiation speed, with the advantage of longer duration of the drug's action ^{166,170} .
1 +	The short-term use of clonazepam at the start of treatment, along with SSRIs can result in faster response ⁷⁰ .
1 +	However, BDZs are associated with a wide spectrum of adverse effects both during and after treatment (dependence, withdrawal syndrome and recurrence if treatment is discontinued) ^{82,98,171} .
2++ 2+	Existing evidence is insufficient to determine whether during pregnancy, the potential benefits of BDZs for the mother outweigh the possible risks to the fetus ¹⁴²⁻¹⁴⁴ .
2++ 2+	There are adverse effects for neonatal infants when prescribed in advanced stages of pregnancy or during nursing (neonatal hypotonia, withdrawal syndrome, sedation, and hypothermia) ^{82,87,146-149} .

Recommendations regarding benzodiazepines for Panic Disorder (PD)

B	If BDZs are used in PD, short-term use is recommended or when crucial due to acute or serious anxiety or agitation, with the lowest possible dosage, which must be reduced gradually.
B	Use for longer periods must always be supervised.
B	Alprazolam, clonazepam, lorazepam, and diazepam are the BDZs recommended for use.
B	To avoid the potential risk of congenital defects, the lowest effective dosage of BDZs should be used, with the shortest possible treatment duration, and as monotherapy if possible. If higher concentrations are required, the daily dosage should be divided into two or three doses, always avoiding use during the first trimester.
√	When prescribing BDZs, patients should be informed of the therapeutic objectives, the duration of the treatment, and the possible side effects.
√	The following should be taken into consideration when prescribing BDZs: age, previous treatments, tolerance, possibility of pregnancy, side effects, patient preferences, and cost as well as effectiveness.

Note: The Technical Dossier from the Spanish Agency for Medications and Healthcare Products (AEMPS)¹⁴² for clonazepam does not include the therapeutic indication for PD.

Other drugs

Other drugs considered in the treatment of PD are:

Azapirones

CPG (RCTS) 1+, SR of RCTS 1++, Meta-analysis 1++ The effectiveness of azapirones (buspirone) in the treatment of PD has not been clearly demonstrated so their use is not recommended^{70,98,102}.

Atypical anti-psychotics

CPG (RCTS) 1-, RCTS 1- Open studies suggest that atypical anti-psychotics olanzapine, quetiapine, and risperidone, added to anti-depressive treatment, may have some benefit in the treatment of refractory PD^{70,155,172}.

CPG (RCTS)
1+/1-

Other⁷⁰

- Pindolol: beta-blocker and antagonist of the 1A serotonergic receptor (5-HT 1A), added to fluoxetine appears to improve symptoms in treatment-resistant PD patients.
- Gabapentine: anti-convulsive with a certain degree of effectiveness in gravely ill patients.
- Sodium valproate (anti-convulsive) and slow-release bupropion (anti-depressant): these have demonstrated a certain degree of effectiveness in open trials.

Until more data becomes available, these drugs should only be used in patients with refractory PD.

CPG (RCTS) 1+ **Not recommended**⁷⁰

Other agents such as tradozone (anti-depressant), propranolol (beta-blocker) and carbamazepine (anti-convulsive) have not been shown to be effective in the treatment of PD, so their use is not recommended.

Evidence regarding other drugs for Panic Disorder (PD)

Azapirones	
1 + 1++	The effectiveness of azapirones (buspirone) in the treatment of PD has not been clearly demonstrated ^{70,98,103} .
Atypical anti-psychotics	
1-	Open studies suggest that atypical anti-psychotics olanzapine, quetiapine, and risperidone, added to anti-depressive treatment, may have some benefit in the treatment of refractory PD ^{70,155,172} .
Other: pindolol, gabapentine, sodium valproate, slow-release bupropion	
1 + 1-	It appears that these may improve symptoms in treatment-resistant PD patients ⁷⁰ .
Not recommended	
1 +	Tradozone, propranolol, and carbamazepine have not been shown to be effective in treating PD ⁷⁰ .

Recommendations regarding other drugs for Panic Disorder (PD)

Other drugs	
B	The use of azapirones (buspirone) is not recommended in the treatment of PD.
√	The use of other drugs such as pindolol, gabapentine, sodium valproate, and slow-release bupropion, due to their indication for refractory PD should be prescribed after the patient has been evaluated by a Centre specialized in Mental Health.
Not recommended	
B	The use of tradozone, propranolol, and carbamazepine is not recommended.

6.3.3. Panic attack

As in the case of psychological interventions, there is minimal evidence regarding acute pharmacological treatment of panic attacks.

In immediate treatment of panic attacks, BDZs have the advantage, in regard to Ads, that its action begins faster. Alprazolam and lorazepam are commonly used in emergency cases. The advantages of sub-lingual use of alprazolam and lorazepam over oral ingestion have not been clearly demonstrated.

RCTS 1+ In terms of pharmacological treatment to maintain benefits, SSRIs and TADs are the treatments of choice. In a study with a duration from 8 to 10 weeks, which included patient groups treated with a placebo, imipramine, or with fluoxetine, it was concluded that the patients treated with either imipramine or fluoxetine showed a statistically significant effect in the reduction of the number of spontaneous panic attacks, compared with the patients treated with the placebo¹⁷³.

Evidence on pharmacological treatment of Panic Attacks

1 +	The use of SSRIs and TADs as the drugs of choice in pharmacological treatment for maintenance of benefits to reduce the number of panic attacks has been demonstrated ¹⁷³ .
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Recommendations on pharmacological treatment of Panic Attacks

√	The BDZs alprazolam and lorazepam may be used for the immediate treatment of serious panic attacks.
B	The use of SSRI and TAD anti-depressants is recommended for pharmacological treatment of panic attacks.

6.4. Combined treatment: psychological and pharmacological therapies

SR of RCTS 1+ A systematic review¹⁷⁴ that analyzes the data from nine RCTS with a sample size of 1,400 individuals, where the participants were patients were diagnosed with anxiety disorders, examines the effectiveness of CBT combined with medication (benzodiazepines, azaspiroones, anti-depressants) in comparison with the effectiveness of each one of these therapies separately, measuring it with different scales (the scale of phobic avoidance, the WP2 anxiety inhibition scale, panic disorder severity scale – PDSS, and the Hamilton anxiety scale – HAM-A). It concludes that there are few studies that are methodologically suited for determining whether combined therapy is better than monotherapy, but those that directly compare combined therapy with pharmacological treatment show that combined treatment is better, which suggests that the use of a cycle of CBT should be considered for patients that have obtained partial response from medications after receiving pharmacotherapy alone. Also, with the exception of PD, adding drugs to CBT appears to not interfere negatively in the effects achieved over the long term with CBT alone.

Evidence on combined treatment (CBT and medication)

1 +	There are few methodologically suitable studies to determine whether combined treatment with CBT and medication is better than each one separately ¹⁷⁴ .
1 +	The few studies that directly compare combined therapy with pharmacological treatment (benzodiazepines, azaspiroones, and anti-depressants) show that combined therapy is better ¹⁷⁴ .
1 +	With the exception of PD, the addition of medication to CBT does not interfere negatively on the effects achieved over the long term with CBT ¹⁷⁴

Recommendations regarding combined treatment (CBT and medication)

A	Combined treatment with CBT and medication is recommended based on its effectiveness, although more comparison studies are needed.
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6.4.1. Generalized Anxiety Disorder (GAD)

RCTS 1+ In one RCTS done in the context of Primary Care and in which psychologists provide CBT in the healthcare facility, CBT was combined with the use of diazepam. The CBT consisted of 7 sessions over a period of nine weeks. The patients received interventions such as cognitive therapy and progressive muscle relaxation, and took work home, working on the technique of exposure to situations and thoughts that generate anxiety. The evaluation of the effectiveness, using the Hamilton scale, continued until six months after the treatment. The study concluded that there is an advantage, in terms of severity and overall change in symptoms, of the combined treatment over the use of diazepam alone, but not over the use of CBT alone. The CBT either alone or in combination with a drug or placebo, showed the lowest incidence of referrals to psychologists and/or psychiatrists at a six-month follow-up.

The authors highlighted the need for more RCTSs that directly compare combined treatment with CBT and treatment with drugs. They also indicate that research should take into account patient preferences, long-term results, and the organizational coordination that the clinical practice reflects.

RCTS 1+,
Pre-post
study 1-,
Non-randomized
controlled study,
1+ In our context, experiences have shown both a direct¹⁷⁶ and indirect^{93,94}, improvement in symptoms when group relaxation and cognitive interventions are added to pharmacological treatment. These interventions are carried out in the healthcare facility, mainly by nursing staff and/or social workers.

Evidence of combined treatment (CBT and medication) for Generalized Anxiety Disorder (GAD)

Application within the scope of Primary Care.	
International	
1+	There is evidence that the combined treatment of CBT and diazepam is superior in terms of severity and overall change in symptoms in comparison with the use of diazepam alone, but not in comparison with the use of CBT alone ¹⁷⁵ .
1+	The CBT reviewed was done by psychologists in Primary Care in 7 sessions over the course of nine weeks, and includes interventions such as cognitive therapy and progressive muscle relaxation. Patients took work home, working on the technique of exposure to situations and thoughts that generate anxiety ¹⁷⁵ .
1+	The CBT either alone or in combination with a diazepam or placebo, showed the lowest incidence of referrals to Specialized Care psychologists and/or psychiatrists at a six-month follow-up ¹⁷⁵ .
2. National	
1+ 1-	There is evidence of effectiveness in terms of the reduction in anxiety symptoms of combined therapies in healthcare centres that include group relaxation and cognitive interventions led by nursing staff and/or social workers ^{93,94,176} .

Recommendations on combined treatment (CBT and medication) for Generalized Anxiety Disorder (GAD)

Application within the scope of Primary Care	
B	The combined treatment of CBT and diazepam or CBT alone, versus the use of diazepam alone, due to its advantage in terms of gravity and overall change of symptoms is recommended, although patient preferences must be taken into account.
B	In combined treatment, such as CBT in healthcare centres, 7 sessions over 9 weeks are recommended, provided by professionals trained in cognitive therapy and progressive muscular relaxation. The patient should also do work at home.
√	In healthcare centres, combined therapy that includes group actions, cognitive therapy, and relaxation is recommended, with at least 8 sessions (1 per week), carried out in a structured manner and directed by trained professionals from the Primary Care teams.

6.4.2. Panic Disorder with or without agoraphobia (PD)

RCTS 1+ The first trials that examine the effectiveness of CBT combined with medication (benzodiazepines, azaspirones, anti-depressants) as compared to the effectiveness of each one of these therapies used separately show that the differences between these treatments are not very clear. Also, during follow-up, it was observed that combined therapy interfered with the maintenance of the benefits obtained long-term by BCT¹⁷⁷⁻¹⁷⁹.

SR of RCTS
1++

Later, a systematic review from the Cochrane¹⁸⁰ that covers this question indicates that increasingly, pharmacological treatment not only tends to show high rates of recurrence when interrupted, but also when adequate dosage is maintained, and that CBT may also be unable to prevent recurrence over the long term. For this reason, combined treatment appears to be practiced quite frequently in real conditions, possibly due to the insufficiency of any of the monotherapies mentioned previously. This review evaluates RCTS that examine the effectiveness and adverse effects of combined treatment, with psychotherapy plus antidepressants, in comparison with either of the two applied separately for treating PD with or without agoraphobia. The results obtained indicate that in the short term, in other words, during the acute phase (2-4 months), combined treatment is more effective than psychotherapy alone or treatment with antidepressants alone, while over the long term, combined treatment is as effective as psychotherapy alone, and is more effective than treatment with anti-depressants alone. The most solid tests in terms of psychotherapy were for CBT, which used techniques of exposure and cognitive restructuring. The analysis of sub-groups with anti-depressants showed similar results for TAGs and SSRIs. The review concluded that either the combination of CBT and pharmacological treatment or CBT alone can be chosen as the first treatment option for panic disorder with or without agoraphobia, depending on the patient's preferences. Treatment with antidepressants alone should not be recommended as a first treatment option when other more appropriate therapies are available¹⁸⁰.

Meta-analysis
1++

Mitte's meta-analysis also studies the effectiveness of combined treatment with CBT and SSRI or tricyclic anti-depressants, and concludes that it is slightly more effective than CBT alone for all of the categories of symptoms, except for quality of life. This study also demonstrates the need for more research to compare, above all, the negative long-term effects of the combination of these treatments with proper blind RCTSs that evaluate all of the aspects of panic syndrome.

RCTS 1+

The intervention models applied in PC in combined treatment with psychological and pharmacological therapy also follow different lines. There is a model based on collaboration between Primary Care and Specialized Care, in which the pharmacological part is directed by the family physician and the CBT part is coordinated and/or handled by a psychotherapist. Three RCTSs based on this model were selected. One RCTS¹⁸¹ evaluated the effectiveness of the combination of anxiolytic medication and CBT as opposed to the use of medication alone. CBT techniques such as relaxation, exposure, behavioral assignment, information on panic attacks, identification of cognitive errors and handling those errors were used. It was found that the combination with CBT, in comparison with the use of medication alone, generates an improvement in indicators such as sensitivity to anxiety, social avoidance, and incapacitation, after 3 months of treatment and at a 12-month follow-up.

- RCTS 1+ There was another RCTS on patients with PD, which combines the use of anti-depressants and/or benzodiazepines with reduced CBT intervention that includes 6 sessions of cognitive-behavioral therapy over the course of 12 weeks, followed by 6 brief telephone contacts in the following 9 months. The patients also received an informational video to prepare them in regard to panic disorder and its treatment, and a revised and condensed version of a manual for doing work at home. The study concluded that the combined intervention produced a sustained and gradually increasing improvement according to the measurement scales used, in comparison with the improvement obtained with pharmacological treatment alone.
- RCTS 1+ Along the same line as the previous ones, another RCTS¹⁸³ compares combined treatments, treatments alone, and with placebo. They all showed better results than the placebo, but the CBT group obtained a more robust and consistent response. CBT, with the treatment provided in 8 sessions over the course of 12 weeks, included techniques of gradual exposure and managing panic, and a treatment manual for patients, which included information on anxiety and panic attacks, and emphasized the importance of patients facing these crises with alternative actions and responses.
- SR of RCTS 1++ There are three lines of future research that deserve additional study. Strategies need to be developed to treat patients who do not respond or who respond only partially to these therapies. Complementary research is also needed with a number of fully-recovered patients, without additional treatment during follow-up, to confirm that combined treatment does not complicate or interfere with psychotherapy over the long term. Lastly, it should be noted that the available data on the effects of the combination of anti-depressants with non-cognitive-behavioral therapies, such as psychodynamic and interpersonal therapies, is limited¹⁸⁰.
- RCTS 1+
pre-post-
study 1-
Non randomized
controlled
study 1+ The studies carried out in our healthcare centers, as already mentioned for treating GAD, indicate the benefit, also in the case of PD, of group relaxation and cognitive interventions, added to pharmacological treatment, in terms of improvement of symptoms^{93,94,176}.

Evidence on combined treatment (CBT and medication) for Panic Disorder (PD)

1++	In the short term, combined treatment of CBT and anti-depressants in comparison with CBT or anti-depressants alone is more effective in improving PD symptoms ¹⁸⁰ .
1++	In the long term, combined treatment of CBT and anti-depressants is as effective as CBT alone and is more effective than treatment with anti-depressants alone ¹⁸⁰ .
1+	During follow-up, combined therapy (combining anti-depressant medication and CBT) interfered in the maintenance of the long-term benefits obtained by CBT alone ¹⁷⁷⁻¹⁷⁹ .
1++	The CBT reviewed used techniques of exposure and cognitive restructuring. The anti-depressants show similar results in the case of tricyclics and SSRIs ¹⁸⁰ .
Application within the scope of Primary Care.	
1. International	
1+	There is evidence of the application of combined treatment with CBT and medication in Primary Care through an integrated model in which general practitioners are supported by specialists and/or psychologists ¹⁸¹ .
1+	Combined therapy in PC* with brief CBT and medication showed a more robust and consistent response than pharmacological treatment alone ^{182,183} . *Note: Brief CBT includes a written manual for the treatment and techniques of exposure and handling panic prepared by psychologists, with an average of 6-8 sessions over the course of 12 weeks. Brief telephone contact is sometimes included. The medication includes anxiolytics and/or anti-depressants.
2. National	
1 + 1-	There is evidence of effectiveness in terms of the reduction in anxiety symptoms of combined therapies in healthcare centres that include group relaxation and cognitive interventions led by nursing staff and/or social workers ^{93,94,176} .

Recommendations regarding combined treatment (CBT and medication) for Panic Disorder (PD)

General recommendations:	
A	The combination of CBT (exposure and cognitive restructuring techniques) and anti-depressants (TADs and SSRIs) is recommended, depending on patient preferences.
A	Treatment with anti-depressants alone is not recommended as first-line treatment, when the appropriate resources to provide CBT are available.
B	In long-term treatments, if anti-depressant drugs are added to the CBT, they should be monitored to ensure that they do not interfere with the beneficial effects of the CBT alone.
Application within the scope of Primary Care	
B	In healthcare centres, in combined treatment, the application of cognitive-behavioral actions is recommended in 6-8 sessions over the course of 12 weeks, provided by trained professionals, through brief CBT that includes techniques of exposure and handling of panic.
√	In healthcare centres, combined therapy that includes group actions, cognitive therapy, and relaxation is recommended, with at least 8 sessions (1 per week), carried out in a structured manner and directed by trained professionals from the Primary Care teams.

6.4.3. Panic attack

The treatment of panic attack is particularly symptomatic, so the recommendations in terms of the combination of psychotherapy and medication to prevent later crises are the same as those already discussed in the combined treatment of PD.

6.5 Other treatments

6.5.1 Self-help treatment

SR and meta-analysis of RCTS 1+ Self-help programs can offers some advantages in treating panic disorders in Primary Care^{184,185}. The most commonly-used alternatives in this type of treatment are bibliotherapy and help using online programs.

Bibliotherapy

Bibliotherapy is defined as the guided use of reading with therapeutic functions and consists basically in the acquisition of knowledge and therapeutic practices by reading a specific bibliography selected and recommended by the therapist.

Manuals that teach methods that are easy to learn and put into practice are used. This type of self-help is considered as a method to complement and facilitate treatment of panic disorders.

CPG (SR and RCTS) 1+ Of the three guidelines selected, the NICE guideline is the one that recommends self-help therapy as one of the treatments of choice for both GAD and for PD, recommending the use of bibliotherapy based on the principles of *CBT*^{81,82}.

SR of RCTS 1+ One systematic review evaluated the effectiveness of treatment of GAD with self-help manuals in Primary Care, comparing this intervention either with educational health brochures or with the waiting list, or with the normal treatment, or with a combination of advice, manual, a certain degree of contact, and *CBT*¹⁸⁶. The review concluded that manuals may be effective in the treatment of GAD, but that there was no evidence of the feasibility and benefits of this procedure. Future research should examine the feasibility of using a self-help manual under guidance and evaluate the benefits of the manuals.

SR of RCTS 1+ Another systematic review that compares self-help interventions that use the principles of *CBT*, with a control group (normal treatment or waiting list) and with relaxation therapy, concluded that self-help is effective in reducing the symptoms (frequency of panic attacks), changing cognitive attitudes related to panic, and impact on quality of life of patients with PD¹⁸⁷. Due to the relatively small size of the studies and their duration, longer RCTSs based on larger and more heterogeneous samples are needed, along with the analysis of the clinical effectiveness and benefits of the interventions. The optimum length of the intervention also needs to be determined for each case, as well as how much professional participation is required to produce a positive change in the patient when this type of intervention is used¹⁸⁷.

Pre-post study 1- There is another intervention study, in a series of cases, on the use of bibliotherapy in Primary Care for patients with mild and moderate anxiety, that highlights the significant improvement after its application, and persistence of the benefits for the following months¹⁸⁸.

RCTS 1+ Another RCTS evaluates the effectiveness of self-help based on the principles of CBT through a manual for patients with mild and moderate anxiety, guided by nursing staff in Primary Care¹⁸⁹. The therapy includes three sessions guided by nurses, two the first week and another during the third month, with patients working at home with a manual and with intermediate tracking through visits or by phone. This method was compared with the normal treatment provided by family physicians, and both were found to have a similar cost and were equally effective in reducing anxiety symptoms, but the patients were more satisfied with the self-help guided by the nurses than the customary treatment.

RCTS 1+ It therefore appears important that certain indications (guidance) are important in the use of bibliotherapy, as the application of this effective self-help without guidance could generate low levels of motivation or fulfillment. The use of short phone calls and/or comments by email can ensure that the bibliotherapy materials are used properly¹⁹⁰.

In our context, the most recent studies done in Spain have concluded, however, that while preliminary results allow for a reasonable degree of optimism, future research is required to more precisely evaluate the clinical effectiveness, persistence of the benefits achieved over the long term, and the optimum selection of materials for each type of patient¹⁹¹.

Bibliotherapy and panic attack

RCTS 1- Bibliotherapy has also been found to be effective in the treatment of panic attacks. In a recent study carried out over 8 weeks, patients with panic attacks were assigned to three types of intervention: bibliotherapy alone, bibliotherapy plus telephone contact, and telephone contact alone. The individuals who received bibliotherapy alone and those that received bibliotherapy plus phone contact significantly reduced their perception of panic and fear when suffering a panic attack. The patients who received bibliotherapy with phone contact also obtained significant reductions in panic symptoms and incapacitation¹⁹².

RCTS 1+ One study evaluated the effectiveness of a program to prevent relapse, consisting of the administration of a self-help manual with monthly telephone contact for patients who had previously followed an intervention with bibliotherapy and monitoring by phone contact. The duration of the intervention was 6 months. Compared with a control group of patients on the waiting list, the individuals who received the relapse-prevention program significantly reduced their measurements of panic attack frequency, panic cognition, anticipatory anxiety, incapacitation, and depression. The results also reflect the importance of contact with the family physician, though brief, for the patients in order to increase motivation in the active participation in bibliotherapy interventions¹⁹⁰.

On-line programs

On-line self-help programs based on the principles of CBT could eventually become a valid alternative for the treatment of anxiety disorders in Primary Care. The recipients of this type of therapy could be patients that due to some type of geographical or personal isolation (such as agoraphobia), have limited access to a direct contact with a psychologist⁶¹, people who have moved or who travel frequently, or those who are familiarized with the use of internet and wish to maintain their anonymity.

SR of different types of studies
1+/2++,
RCTs 1+

Some reports and trials highlight this option as an effective and cost-effective approach, although it must be noted that the evidence is minimal and RCTs with easy-to-use programs are required, with comparison to other types of self-help such as bibliotherapy, with placebos, or with individual or group CBT, both short and long term^{33,193-197}. In any case, it appears that these programs could be a valid and acceptable alternative in the context of Primary Care, helping to respond to the high demand for psychological treatment, especially in these patients.

Evidence on self-help for Generalized Anxiety Disorder (GAD), Panic Disorder (PD), and Panic Attack

1 +	There is evidence of the application and effectiveness of bibliotherapy as self-help therapy, based on the principles of CBT, in the treatment of GAD and PD in Primary Care ^{70,81,82} .
1 +	A self-help program with bibliotherapy based on the principles of CBT directed by nursing staff in Primary Care, with three on-site sessions, work at home with a manual, and intermediate monitoring with visits or phone calls, has been shown to be effective in the treatment of patients with mild and moderate anxiety ¹⁸⁹ .
1 + 1-	Bibliotherapy has been shown to be effective in the treatment of patients with panic attacks, reducing the perception of panic, fear of suffering a crisis, panic symptoms, and incapacitation ^{187,192} .
1 +	The use of bibliotherapy in the context of relapse-prevention programs (self-help manual and monthly telephone contact over the course of 6 months) reduces the frequency of panic attacks, panic cognition, anticipatory anxiety, incapacity, and depression ¹⁹⁰ .
1 +	Contact with the family physician, though brief, generates greater active participation in bibliotherapy interventions ¹⁹⁰ .
1 + 2++	Online self-help program based on CBT appear to be cost-effective, but more CBSs are required to compare this with other types of self-help, such as bibliotherapy, placebo, and with individual or group CBT over both the short and long term ^{33,193-197} .

Recommendations regarding bibliotherapy for Generalized Anxiety Disorder (GAD), Panic Disorder (PD), and Panic Attack

B	The application of bibliotherapy is recommended based on the principles of CBT in public healthcare centres, by trained professionals using self-help manuals and telephone contact or brief personal contacts.
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6.5.2. Herbal medicine

In recent years, studies on the usefulness of herbal remedies to treat mild and moderate anxiety have proliferated. Medicinal herbs are popular, used worldwide, and could be considered as an option in the treatment of anxiety if they can be proven to be effective and safe. Family physicians need to know how to recognize both the benefits and risks in these formulations. This would avoid the attitudes of rejection that could be transferred to the patient if their use is hidden from the patient, masking possible adverse effects¹⁹⁸.

Kava kava (*Piper methisticum*)

Meta-analysis 1+ Kava is a beverage prepared from the rhizome of the Kava oceanica plant and has been used for centuries for ceremonial and medicinal purposes.

In the sixties, some non-controlled clinical studies indicated that kava could be beneficial in the treatment of anxiety. A systematic review confirmed these findings, indicating a significant reduction of 9.7 points on the total points on the Hamilton anxiety scale (HAM-A) in favor of kava in comparison with a placebo.¹⁹⁹

SR of RCTS 1+ The review cited earlier was updated with data from an RCTS, concluding that kava extract appears to be an effective option in the symptomatic treatment of anxiety in comparison with the placebo. The adverse effects indicated in the included RCTSs also indicate that this extract is relatively innocuous in short-term treatment (1 to 24 weeks), but the review concluded that additional and more rigorous studies on kava's long-term effectiveness and harmlessness were required²⁰⁰.

RCTS 1+ The doubts regarding kava's effectiveness continue to motivate different studies. There is an RCT that dissents in regard to its effectiveness and does not reveal any difference between its use and a placebo in anxiety disorders such as GAD²⁰¹. But the sample size and duration of the study (four weeks) is very small. Other RCTS have demonstrated that Kava needs to be used for a longer time (eight weeks) to show its effectiveness¹⁹⁸; its use may be as effective as buspirone or opipramol for acute treatment of GAD²⁰² and significantly improves sleep disorders associated with anxiety disorders²⁰³.

RCTS 1+, Series of cases 3, Legal regulations It continues to be the object of controversy regarding its safety of usage²⁰⁴. There are RCTS that focus more on the side effects associated with hepatic toxicity; the FDA has issued warnings in this regard²⁰⁶, , and the Spanish Agency for Medications and Healthcare Products (AEMPS) includes it in the list of plants whose sale to the public is prohibited or restricted due to its toxicity²⁰⁷. Later studies have emphasized the quality of the formulations, and suggest that inclusion, without a standard process, of the plant's bark increases the level of hepatic toxicity¹⁹⁸. It is important to consider the possible interactions with other drugs and with other medicinal herbs, and in this sense, the RCTS conclude that the dosage and quality of the formulations must be monitored in order to prevent cases of intoxication. For patients with mild or moderate anxiety who want to use natural remedies and do not drink alcohol or use other drugs that could be metabolized by the liver, short-term use of kava appears to be acceptable¹⁹⁸.

Valerian (*Valeriana officinalis*)

SR of RCTS 1+ Valerian is one of the most widely-used medicinal herbs for insomnia, and it is also used for treating anxiety. It is used in dried herb form, as an extract, or tincture.

On review studied the effectiveness and safety of valerian in treating anxiety disorders²⁰⁸. The review included an RCT with patients who suffered from GAD. This was a pilot study, with a duration of four weeks, with valerian, diazepam, and placebo. The review concluded that since it was based on a single small study, there was insufficient proof to draw conclusions regarding the effectiveness or safety of valerian in comparison with the placebo or diazepam for GAD. RCTS that include larger samples and that compare valerian with a placebo or other interventions used to treat anxiety disorders such as anti-depressants are needed.

Passion flower (*Passiflora caerulea*)

Passion flower (passion flower extract) is a popular remedy used for anxiety. It has been used for many years in the US and has not been associated with any chronic or acute toxic effects. It is available for oral use, mainly in the form tablets made from the dried herb or as an infusion. The variation in the preparation, depending on the different formulations produced by manufacturers, makes it even more difficult to compare the effectiveness of the different products.

SR of RCTS 1+ One systematic review included an RCT with patients with GAD, studying the effectiveness and safety of passion flower in the treatment of anxiety, comparing oxazolam with passion flower over a period of four weeks^{209,210}. The evidence of this small study shows a similar response model for passion flower and benzodiazepines in the evaluation in short-term treatment of GAD; but the number of randomized controlled studies that examine the effectiveness of passion flower for this disorder is too small to allow clear conclusions to be drawn. Nor are there any comparisons of passion flower with the drugs most commonly used for the treatment of generalized anxiety, anti-depressants, which limits the ability to draw any useful conclusions for clinical practice.

Ginkgo biloba (*Ginkgo biloba L.*, *Salisburia adiantifolia Smith*)

RCTS 1+ Extract of Ginkgo Biloba is extracted from the leaves and seeds of the Ginkgo Biloba tree. It has been used for years because of its therapeutic actions.

One RCT has demonstrated its effectiveness in patients with GAD, significantly reducing anxiety according to the Hamilton scale, comparing it with a placebo. It is also tolerated well (the adverse effects were mild-moderate in nature, related to allergic reactions or a drop in systolic blood pressure readings), shows no risk of dependence, and apparently does not alter cognitive functions²¹¹.

More studies and longer-term studies are needed to confirm the data obtained.

Yellow globeflower (*Galphimia Glauca*)

RCTS 1+ Yellow globeflower is a plant used in traditional Mexican medicine as a “nervous tranquilizer”. One RCT compared its effectiveness, safety, and tolerability with lorazepam in patients with GAD over the course of 4 weeks. Both treatments were found to be effective and safe anxiolytics, with the plant extract tolerated better²¹².

Formulation of whitethorn (*Crataegus Oxyacanta*), California poppy (*Eschscholtzia californica*) and magnesium

Whitethorn is a small thorny tree with abundant leaves. Its therapeutic history is quite recent and it has been called the “heart plant”. The California poppy belongs to the same family as the poppy and has sedative and hypnotic properties.

RCTS 1+ A formulation with the extracts from both plants combined with magnesium in fixed amounts has been demonstrated in one RCT to be better than a placebo at reducing mild or moderate anxiety in patients with GAD. It appears that the difference with the placebo increases over the course of treatment, but longer-term studies are needed to confirm this trend. The side effects were associated with digestive disorders and mild-moderate psychological disorders, so the researchers concluded that the formulation could be effective and safe for symptomatic treatment in clinical practice of mild-moderate states of anxiety²¹³.

Evidence on treatment using medicinal herbs for Generalized Anxiety Disorder (GAD) and Panic Disorder (PD)

1+, 3	Kava extract, in comparison with the placebo, appears to be an effective option in short-term symptomatic treatment (1 to 24 weeks) of anxiety, although the FDA and the Spanish Agency for Medications and Healthcare Products have warned of its hepatic toxicity ^{199,200,205-207} .
1 +	There are insufficient studies to draw conclusions regarding the effectiveness or safety of valerian in the treatment of GAD. ²⁰⁸
1 +	Passion flower has been demonstrated to have a certain degree of effectiveness in the short-term treatment of GAD ^{209,210} .
1 +	Other herbs (ginkgo biloba, yellow globeflower) and the combination of whitethorn, California poppy, and magnesium appear to be effective in the short-term treatment of GAD ²¹¹⁻²¹³ .

Recommendations regarding treatment using medicinal herbs for Generalized Anxiety Disorder (GAD) and Panic Disorder (PD)

B, D	Due to its hepatic toxicity, kava* is recommended only for short-term use and for patients with minor or moderate anxiety who prefer to use natural remedies, provided that they do not have any prior hepatic alterations, do not consume alcohol, or use other medications metabolized by the liver, with medical supervision required.
B	There are not sufficient studies on the effectiveness of valerian, passion flower, ginkgo biloba, yellow globeflower, and the preparation of whitethorn, California poppy, and magnesium to encourage their use.
√	Professionals are advised to ask patients regarding any other herbal medicinal products that they are taking or have taken.

* In 2004, the Spanish Agency for Medications and Healthcare Products (AEMPS)¹⁴² included kava in the list of plants prohibited or restricted for sale to the public due to its hepatic toxicity.