Clinical Practice Guideline for Treatment of Patients with Anxiety Disorders in Primary Care

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH AND CONSUMER AFFAIRS

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y CONSUMO

Plan de Calidad para el Sistema Nacional de Salud

SaludMadrid
Agencia Laín Entralgo para la Formación, Investigación y Estudios Sanitarios
Comunidad de Madrid

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This CPG is a healthcare decision making support. It is not mandatory, and it is not a substitute for the clinical judgement of healthcare personnel.

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Official presentation

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Care practice is becoming more and more complicated due to many different factors. One of the most relevant factors is the exponential increase of scientific information.

To make clinical decisions that are adequate, safe and effective, practitioners need to devote a lot of effort in continuously updating their knowledge.

In 2003, the Interterritorial Council of the Spanish NHS created the GuiaSalud Project whose final aim is to improve clinical decision-making based on scientific evidence, via training activities and the configuration of a registry of Clinical Practice Guidelines (CPGs). Since then, the GuiaSalud project has assessed dozens of CPGs in agreement with explicit criteria stipulated by its scientific committee, it has registered them and has disseminated them over the Internet.

At the beginning of 2006, the Directorate General of the Quality Agency of the National Health System prepared the Quality Plan for the National Health System, which was divided into 12 strategies. The purpose of this Plan is to increase the cohesion of the National Health System and help guarantee maximum quality health care for all citizens regardless of their place of residence.

Within that context, the GuiaSalud Project was renewed in 2007 and the Clinical Practice Guideline Library was created. This project developed into the preparation of the CPGs and included other Evidence-Based Medicine services and products. It also aims to favour the implementation and assessment of the use of CPGs in the National Health System.

A first step was to commission different agencies and expert groups in prevalent pathologies related to health strategies to prepare eight CPGs. This Anxiety guideline is the consequence of this assignment.

The definition of a common methodology to prepare the CPG for the NHS was also requested and this has been prepared as a collective effort of consensus and coordination among the Spanish CPG expert groups. This methodology was used as the basis to prepare this Anxiety guideline and the other CPGs driven by the Quality Plan.

It is widely acknowledged that mental disorders constitute a significant social and economic burden due to their frequency, coexistence, and comorbidity, in addition to the disability that they generate.

Within the area of mental health problems, anxiety disorders are associated with high levels of disability and have a considerable impact on personal well-being as well as on social and labour relations. The aggravating factor of the prevalence of these disorders and the recurrent or even chronic nature of many of these disorders makes them as incapacitating as any other chronic illness.

Anxiety disorders, alone or associated with other pathologies, are one of the most frequent causes of Primary Care visits, and there is a certain degree of variability in how they are managed. The lack of a common pattern of manifestation, somatisation and association with chronic illnesses, as well as the need for specific therapy sometimes prolonged over time, increases the complexity of the treatment of these patients.

The purpose of the *Clinical Practice Guideline for Treatment of Patients with Anxiety Disorders in Primary Care* is to provide professionals with practical recommendations based on scientific evidence to assist in the detection and effective treatment of these disorders, offering the ideal therapeutic alternatives in each process. The professionals involved in providing care,

as well as the patients themselves and scientific organizations were involved in the preparation of this guideline, which seeks to improve the care provided to patients with anxiety disorders and the quality of life of those patients.

Dr. Alberto Infante Campos
General Director of the Quality Agency of the NHS

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Spanish Neuropsychiatry Association (AEN)

Madrid Panic and Agoraphobia Association (AMADAG)

Spanish Confederation of Family Groups and Individuals with Mental Illness (FEAFES)

Madrid Federation of Mental Health Associations (FEMASAN)

Spanish Society of Primary Care Physicians (SEMERGEN)

Spanish Society of Family and Community Medicine (SEMFYC)

Spanish Psychiatric Society (SEP)

Madrid Society of Family and Community Medicine (SoMaMFYC)

Spanish Union of Scientific Nursing Societies (UESCE)

Members of these societies have taken part in the development and external review of this Clinical Practice Guideline.

Conflict of Interest Statement: All of the members of the Working group, as well as all of the people who took part in the external review have signed the declaration of interest included in Appendix 6.

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Questions to be answered

Definition, clinical features, and classifications

- What is the definition of anxiety as a symptom/syndrome?
- What is the definition of anxiety as a specific clinical profile?
- How are anxiety disorders classified?

Diagnostic criteria

- What are the diagnostic criteria of the different anxiety disorders?
- What are the criteria for suspecting anxiety disorders?
- What studies should be done initially with adults suspected to suffer anxiety disorders in order to allow early detection?
- Are there key questions that could help Primary Care professionals to detect anxiety disorders in patient interviews?
- What are the differential diagnoses to be taken into account?

Treatment

- What is the most effective treatment for generalized anxiety disorder?
- What is the most effective treatment for panic disorders?
- What is the most effective treatment for panic attacks?

Information/communication with patients

- What is the basic information that should be given to patients with anxiety disorders?
- What is the basic information that should be given to the families of patients with anxiety disorders?
- What is the best way to inform patients of their disorders?

Diagnostic and therapeutic strategies

- What are the steps to be followed in response to an anxiety disorder (GAD, PD, and panic attack)?
- What are the criteria for referral from Primary Care to Mental Health?

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Dissemination and implementation

- What is the strategy to distribute and implement the guideline?
- What are the indicators for tracking the key recommendations?

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Summary of recommendations

Psychological treatment

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 Care teams.

Psychological techniques applicable in the context of Primary Care for Generalized Anxiety Disorder (GAD)

√	Brief actions in PC should be carried out by trained professionals and 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.
√	The following are recommended as psychological techniques for possible application in PC to reduce anxiety symptoms associated with GAD: techniques for relaxation, exposure, self-control, training in social skills, self-instruction, training in treatment anxiety, cognitive distraction and thought stoppage, resolution of problems, cognitive restructuring, and interpersonal therapy.

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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 treatment 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 *in vivo* exposure.
Primary Care	
B	The application of cognitive-behavioral actions are 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.

Psychological techniques applicable in the context of Primary Care for Panic Disorder (PD)

√	Brief actions in PC should be carried out by trained professionals and 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.
√	The following are recommended as psychological techniques for possible application in PC to reduce anxiety symptoms associated with PD: techniques for relaxation, exposure, self-control, training in social skills, self-instruction, training in treatment anxiety, cognitive distraction and thought stoppage, resolution of problems, cognitive restructuring, and interpersonal therapy.

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

√	The following psychological techniques are recommended in PC to control symptoms related to panic attacks. • Behavioral and support measures that include psycho-education: calm the patient and advised actions in writing. • Training in the treatment of symptoms: teaching of relaxation techniques and learning breathing exercises to handle hyperventilation. • Exposure techniques.
√	The family should be informed regarding the type of actions to help in resolving any new attacks.

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Pharmacological treatment

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	In terms of anti-depressants recommended for use, SSRI (paroxetine, sertraline, or escitalopram), SNSRI (slow-release venlafaxine) 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 fetus.
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.

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 fro the response to treatment with anti-depressants or CBT.
B	The use of the BDZs alprazolam, bromazepam, lorazepam, and diazepam is recommended.
B	To avoid the potential risk of congenital defects, the lowest effective dosage of BDZ 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 BDZ: age, previous treatments, tolerability, possibility of pregnancy, side effects, patient preferences, and cost as well as effectiveness.

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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 BDZ, although its use is very limited in Spain.
√	The use of other drugs such as pregabline, 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.

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 (cytalopram, escytalopram, 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.

Note[142]:

- 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.

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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	The BDZs alprazolam, clonazepem, lorazepam, and diazepam are recommended.
B	To avoid the potential risk of congenital defects, the lowest effective dosage of BDZ 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 for Panic Disorder (PD)

Other drugs	
B	The use of azapirones (buspirone) is not recommended for treating PD.
√	The use of other drugs such as pindolol, gabapentin, sodium valproate, and slow-release bupriopion, 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, propanolol, and carbamazepine is not recommended.

Pharmacological treatment for Panic Attack

√	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.

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Combined treatment: psychological and pharmacological

Combination 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 advantages 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.

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 treatment 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.

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Other treatment: bibliotherapy and herbal medicines

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.

Herbal Medicine 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.

Information/communication with the patient*

Information/communication with patients with Generalized Anxiety Disorder (GAD), Panic Disorder (PD), and/or Panic Attack

√	Information for the patient should form part of the integrated treatment of anxiety disorders at the Primary Care level.
D	The patient, and when appropriate, the family, should be given information based on the evidence regarding their symptoms, treatment options, and the possibilities of treating their disorders, taking patient preferences into account to facilitate joint decision-making.
D	A contact style based on empathy and understanding is recommended to improve patient satisfaction.
D	The possibility of family support should be assessed, taking into account the available social resources, and suggesting the most appropriate changes in lifestyle.

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* Source: Workgroup for the Clinical Practice Guideline for the Treatment of Patients with Anxiety Disorders in Primary Care. Clinical Practice Guideline for Treatment of Anxiety Disorders in Primary Care. Madrid: National Plan for the NHS of the MSC. Health Technology Assessment Unit. Agencia Lain Entralgo. Region of Madrid: 2008. Clinical Practice Guid: HTAU Nº 2006/10.

1. Introduction

This document is the *complete* version of the CPG for treatment patients with anxiety disorders in Primary Care. The CPG is structured into chapters which respond to the questions that appear at the start of each one. A summary of the evidence and recommendations are presented at the end of each chapter. The right margin will include an indication of the type of study and the possibility of bias of the bibliography reviewed.

The material that provides a detailed description of the methodological process applied for the CPG (description of the techniques used in qualitative research, search strategy for each clinical question, guideline table) is available at the *GuiaSalud* website, as well as in the *UETS*, the Health Technology Assessment Unit of the Agencia Laín Entralgo. These websites also include the *Methodology Manual for CPG preparation*, which covers the general methodology used [1]. There is also a *summarized* version of the CPG, which is shorter and includes the main appendices of the *complete* CPG, a *quick* guideline with the main algorithms and recommendations and an informational *brochure* for patients. These versions are available on both the aforementioned websites as well as in the printed edition.

Prevalence of anxiety and associated burdens

Mental health, as an indivisible part of health, contributes significantly to quality of life and full social participation. Mental disorders constitute a significant social and economic burden due to their frequency, coexistence, and comorbidity, in addition to the disability that they generate. Mental illness is the second leading cause of illness in societies with market economies, with these figures expected to increase considerably [2] with few prospects for control.

In our context, it has been confirmed to be one of the categories of causes that most contribute to the loss of illness-free years of life, using the DALY rate (Disability-Adjusted Life Years)[3] as the measure of the burden of illness. For this reason, mental health has required special attention by the agents involved, reflected by the broad lines of action in the document "*Mental Health Strategy for the National Health System*"[4]: healthcare for patients, coordination amongst institutions, scientific societies, and associations, training of healthcare personnel, promotion of research and systems of information and evaluation.

With mental health problems, *anxiety disorders* are associated with significant levels of disability [5]. This dysfunctionality has a considerable impact on personal well-being, on social relations, and on productivity on the job, with the aggravating factor that its prevalence and the recurrent or even chronic nature of many of these disorders makes them as debilitating as any other chronic physical illness.

Anxiety disorders, along with mood disorders, are the disorders that contribute most to morbid-mortality through the suffering that they generate and are the ones that have the biggest repercussions on national economies [6-8]. Pathological panic-anxiety makes it difficult for the subject to function anywhere, limiting autonomy, and leaving the person trapped and threatened by the panic itself.

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In our context, most studies put the prevalence of mental illness in the general population at between 10% and 20%[9,10]. Figures from the Eurobarometer give an estimated prevalence for any mental disorder in Spain of 17.6%, higher in women (20.8%) than in men (14.2%)[11]. The most frequent disorders are normally anxiety, followed by depression, or vice-versa, depending on the classification used and whether or not the analysis includes phobias.

The international prevalence of anxiety disorders varies widely among the different epidemiological studies published, although the variability associated with anxiety disorders considered overall is significantly lower than the variability associated with the disorders considered individually. There are several factors that explain the heterogeneity of the percentages in these studies, such as the diagnostic criteria for inclusion, the diagnostic instruments, the size of the sample, the country covered by the study, and the response percentage. The estimated percentages of prevalence-year and prevalence-life for anxiety disorders were 10.6% and 16.6% respectively [12]. If the studies are done among users who visit Primary Care facilities, the prevalence increases, varying between 20% and 40%[5,6,10,13,14]. Anxiety disorders in and of themselves or associated with other pathologies are one of the most frequent causes of Primary Care visits and represent one of the main health problems in Spain. In the context of Spain, the prevalence of anxiety disorders in the community, with the precision difficulties mentioned before, varies around 2.3%-8.9%[9], reaching figures between 9% and 19.5%[5,8,10,14] when we talk about patients who visit a healthcare centre because they have the perception that they do not feel good.

Women have a higher risk than men of suffering anxiety disorders [11, 15], and the prevalence of most of the anxiety disorders in the case of women is double the prevalence for men, except in the case of social phobia, in which the differences are smaller. The age at which anxiety disorders start is lower than for depression disorders. This appears to indicate that many people who show signs of anxiety disorders during childhood, adolescence and early years of adulthood, have a higher risk of developing a depression disorder later in life. This means that a therapeutic approach to anxiety disorders could prevent the later appearance of depression disorders [11,15] (See tables 1-3).

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Table 1. Prevalence-year of anxiety disorders following the criteria DSM-IV (data weighted for the Spanish population). 2001 - 2002

Anxiety disorders						
	Total		Men		Women	
	Prev (%)	CI 95%	Prev (%)	CI 95%	Prev (%)	CI 95%
Generalized anxiety	0.50	(0.30-0.70)	0.44	(0.11-0.78)	1.18	(0.81-1.56)
Social phobia	0.60	(0.33-0.87)	0.57	(0.13-1.00)	0.64	(0.32-0.95)
Specific phobia	3.60	(2.82-4.38)	1.19	(0.68-1.70)	4.20	(3.23-5.16)
Post-traumatic stress disorder	0.50	(0.30-0.70)	0.25	(0.02-0.48)	0.94	(0.50-1.39)
Agoraphobia	0.30	(0.10-0.50)	0.15	(0.02-0.29)	0.60	(0.26-0.95)
Panic disorder	0.60	(0.40-0.80)	0.38	(0.14-0.63)	0.98	(0.60-1.36)
Any anxiety disorder	6.20	(4.63-7.77)	2.53	(1.74-3.31)	7.61	(6.41-8.80)

CI: confidence interval.

Source[15]: Study ESEMeD-España.

Table 2. Prevalence-life of anxiety disorders following the criteria DSM-IV (data weighted for the Spanish population). 2001 - 2002

Anxiety disorders						
	Total		Men		Women	
	Prev (%)	CI 95%	Prev (%)	CI 95%	Prev (%)	CI 95%
Generalized anxiety	1.89	(1.49-2.29)	1.15	(0.64-1.66)	2.57	(1.49-3.16)
Social phobia	1.17	(0.81-1.54)	0.06	(0.51-1.61)	1.28	(0.83-1.73)
Specific phobia	4.52	(3.82-5.23)	2.32	(1.60-3.05)	6.54	(5.38-7.69)
Post-traumatic stress disorder	1.95	(1.18-2.73)	1.06	(0.00-2.2)	2.79	(1.71-3.87)
Agoraphobia	0.62	(0.36-0.89)	0.47	(0.08-0.86)	0.76	(0.39-1.14)
Panic disorder	1.70	(1.32-2.09)	0.95	(0.53-1.37)	2.39	(1.76-3.02)
Any anxiety disorder	9.39	(8.41-10.37)	5.71	(4.57-6.85)	12.76	(11.24-14.29)

CI: confidence interval.

Source[15]: Study ESEMeD-España.

Table 3. Prevalence-year of anxiety disorders classified according to DSM-IV by age group in the Spanish population. 2001 - 2002

Age	Any mental disorder	Anxiety disorder
	Prevalence (CI 95%)	Prevalence (CI 95%)
18-24 years old	10.1 (7.3-12.9)	7.8 (5.3-10.4)
25-34 years old	8.5 (6.3-10.8)	4.2 (2.9-5.6)
35-49 years old	8.4 (6.6-10.2)	4.5 (3.2-5.8)
50-64 years old	9.1 (6.8-11.3)	6 (4.3-7.7)
Over 65 years old	6.6 (5.1-8.1)	3.9 (2.8-5.0)

CI: confidence interval.

Source[15]: Study ESEMeD-España.

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Variability in clinical practice

Patients with mental disorders or chronic psychosocial conflicts repeatedly visit the different healthcare facilities, especially at the level of primary care, mainly due to quick access and the longitudinality of the care [5,8,16,17].

In general, mental health problems are normally treated initially in Primary Care facilities, and a significant number of the requests generated by these pathologies are resolved at this level [18,19].

Family physicians are the healthcare professionals, due to their position in the healthcare network, can detect the first psychiatric symptoms earlier in patients who visit their offices with an anxiety disorder. Some of the studies done in our context indicate a low level of detection of psychiatric disorders, with the prevalence of the detected disorders ranging between 18%-27% versus 36%-47% of probable pathology [9,13,14]. The lack of a common pattern in the presentation of different anxiety disorders, somatization and association with chronic illnesses, as well as the limitation of time in family medicine facilities are some of the reasons that complicate diagnosis within the scope of Primary care [20,21].

Anxiety and panic are very frequent symptoms in doctor visits, and they are very often unspecific and can be masked somatically. This makes the treatment of patients with anxiety disorders complex, especially if we take into account the difficulty of differential diagnosis, the need for specific therapeutic treatment that at time is extended over time for each form of the illness, as well as the need at time for referral to Specialized Care when the etiology, disorder, or manifestations of the illness require it.

All of these factors generate a certain degree of variability in the treatment of anxiety disorders. A study done in Spain, with data from three regions, evaluates the main factors that influence the therapeutic attitudes of doctors in connection with anxiety disorders and the variability in how they are approached. The type of anxiety disorder was the determining variable for the type of therapy selected the referral criteria. The probability of referring patients increased when there was a prior diagnosis of anxiety. Patients with phobic anxiety, panic, or mixed anxiety were more than twice as likely to be referred as patients with generalized anxiety. In general, pharmacological treatment was done with appropriate and specific drugs, with a high degree of variability that depended mainly on the type and other characteristics of the process, the patient, and the professional [22].

The variability in the approaches to anxiety disorders is also the result of an enormous variability in training. Different studies have identified a significant need for continuous training in mental health for Primary Care doctors, particularly in the field of psychiatric interviews and the knowledge, abilities, and attitudes to provide "psychological assistance", especially in regard to somatization disorder, psychosexual problems, treatment of stress [17,23-28].

In terms of the use of non-medication treatments, these are covered in a minimal number of studies, although the low use of psychological actions with proven effectiveness is significant [6]. There are even fewer studies evaluating the work done by Primary Care social workers and nursing staff. These professionals play a very important role in the therapeutic treatment of anxiety disorders at the primary care level, providing both individual and group therapy, with techniques that can be implemented in Primary Care provided that the professionals involved have received the necessary training.

The search for a common pattern for the detection and treatment of pathological anxiety in a Primary Care facility is not a simple task. This is due in part to the wide variety of official diagnostic categories that exist, the relatively sort duration of office visits, the frequent somatization

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and association of this type of disorders with other chronic illnesses. For this reason, many studies have concluded that one of the basic needs is to provide general practitioners with clear, practical clinical guides based on scientific criteria to assist them in effectively detecting and treating anxiety disorders, offering the ideal therapeutic alternatives in each process, at the care level in which they are available [7,8,29].

This guideline is therefore intended to be a useful tool for all professionals who work at the Primary Care level and for patients with these anxiety disorders, including an appendix with specific information for patients that was prepared with input from patients.

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2. Scope and objectives

The main objective of this guideline is to orient healthcare professionals in the area of *Primary Care (PC)*, on one hand in *the recognition of anxiety disorders* in *adult* patients, and on the other, in the selection of recommendations based on the available scientific evidence on *therapeutic actions for treating adult patients* with anxiety disorders that are treatable from the point of view of Primary Care, *generalized anxiety disorder (GAD)*, and *panic disorder (PD), with or without agoraphobia.* This objective involves an improvement in the quality of the care in the treatment of this process, to consequently improve the quality of life of these patients.

The guideline is therefore aimed at healthcare professionals involved in treatment patients with anxiety disorders and who work in the area of Primary Care (doctors, nursing staff, social workers) and is also aimed at patients who suffer these anxiety disorders and who turn to primary care. For the latter, it is a tool that allows them to know the possible strategies and therapies for their illnesses, so that they can avoid treatments that are not supported by scientific evidence.

The guideline presents different therapeutic alternatives (pharmacological and non-pharmacological treatment) that can be used in Primary Care depending on the available resources. In fact, the resources that are currently available were taken into consideration before the final preparation of the recommendations.

This guideline does not directly cover recommendations for anxiety disorders other than generalized anxiety disorder or panic disorder in adults. Since this guideline is focused nationally, it does not cover organizational questions, but rather tries to establish a basic circuit for patients between the two levels of healthcare – Primary Care and Specialized Care – so it will also be distributed among the other professionals involved in providing patient care in an effort to provide integrated care of patients.

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3. Methodology

The methodology used is covered in the *CPG preparation manual* from the Ministry of Healthcare and Consumption [1].

The steps that were followed were:

- Creation of the group to create the guideline, made up of professionals from: Primary Care (general practitioners, nurses, social workers), Specialized Attention (psychiatrists, psychologists, and nurses), and technicians from the Health Technology Assessment Unit (UETS). A patient with an anxiety disorder also participated in the preparation of this guideline as part of the guideline development group, from the initial work phases.
- Formation of a sub-group, with members from the Guideline development group, to prepare information aimed at the patients.
- Definition of the guide's scope and objectives, including the social view of the illness using qualitative research techniques. Different healthcare professionals were contacted (Primary Care doctors and Specialized Care doctors) and with the help of a questionnaire, the resources of participant observation, and in-depth interviews, information was gathered on the social, demographic, and health conditions, in addition to the healthcare path and treatment of patients with anxiety disorders who were treated by those professionals. A discussion group was also formed with anxiety disorder patients who voluntarily participated to openly express their interests in the treatment of their illnesses.
- Formulation of clinical questions following the Patient/Intervention/Comparison/Outcome format (PICO).
- Bibliographic search in: Medline, Embase, Pascal Biomed, CINAHL, Cochrane Plus, DARE, HTA, Clinical Evidence, INAHTA, NHS EED, CINDOC. Languages: Spanish, English, and French. Study population: adults. Publication year limitation: only for primary studies. First a search was done to locate practical clinical guides (CPGs) and their quality was evaluated using the AGREE instrument. Three CPGs were included as secondary source of evidence in response to specific sections of the guideline (treatment, information/communication with the patient, and diagnostic and therapeutic strategies). In phase two, a search was done for systematic revisions, meta-analyses, and evaluation reports in the databases mentioned earlier. In phase three, an expanded search was done on primary studies (clinical tests, observational studies, diagnostic and prognostic test studies).
- Evaluation of the quality of the studies and summary of the evidence for each question following the recommendations of SIGN (Scottish Intercollegiate Guidelines Network).
- Formulation of recommendations based on SIGN's "formal evaluation" or "reasoned judgment". Controversial recommendations or those lacking evidence were resolved by consensus of the creation group.
- The guideline was reviewed externally by a group of professionals selected for their knowledge on the methodology of preparing guides, the pathology covered, and the scope of application. The different Scientific Societies involved were contacted: Spanish Family and Community Medicine Society (SEMFYC), Spanish Society of Primary Care Physicians (SEMERGEN), Madrid Society for Family and Community Medicine (SoMaMFYC), Spanish Psychiatry Society (SEP), Spanish Neuro-psychiatry Association (AEN) and the Spanish Union of Scientific Nursing Societies (UESCE). In the case of patient participation, the Spanish Confederation of Family Groups and People with Mental Illnesses

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(FEAFES), the Madrid Federation of Mental Health Associations (FEMASAN), and the Madrid Panic and Agoraphobia Association (AMADAG). All of these societies were represented either as members of the guideline development group or as external reviewers.

- The material that provides the detailed information on the methodology applied to prepare the CPG (description of the techniques used in the qualitative research, the search strategy for each clinical question, guideline table) is available at www.guiasalud.es.

Updates to the Guideline

The UETS, which is responsible for publishing the Guideline, will also be in charge of updating it within 3 to 5 years, or earlier, depending on the new evidence that becomes available. This update will be done by adding the updated bibliographic searches and will focus especially on the aspects in which recommendations may undergo significant modifications.

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4. Definition, clinical features and classifications

This chapter will answer the following questions:

- What is the definition of anxiety as a symptom/syndrome?
- What is the definition of anxiety as a specific clinical profile?
- How are anxiety disorders classified?

4.1. Normal and pathological anxiety

Anxiety can be defined as the anticipation of future harm or misfortune accompanied by a feeling of dysphoria (unpleasantness) and/or somatic symptoms of tension. The objective of the anticipated harm may be internal or external. It is an alert signal that can warn of imminent danger and allows the person to take the necessary measures to confront a threat.

It is important to understand anxiety as a normal feeling or emotional state in response to certain situations and that it constitutes a common response to different daily stressful situations. This means that a certain degree of anxiety is even desirable for the normal treatment of day-to-day demands. Only when this exceeds a certain intensity or the person's adaptive capacity does anxiety become pathological, causing significant discomfort with symptoms that affect the person physically, psychologically, and behaviorally (table 4).

Table 4. Symptoms of anxiety: physical and psychological

Physical symptoms	Psychological and behavioral symptoms
Vegetative: sweating, dry mouth, dizziness, instability	Worry, apprehension
Neuromuscular: trembling, muscular tension, headache, paresthesia	Feeling of oppressiveness
Cardiovascular: palpitations, accelerated heartbeat, precordial pain	Fear of losing control, of going crazy, or the feeling of imminent death
Respiratory: dysnea	Difficulty concentrating, complaints of memory loss
Digestive: nausea, vomiting, dyspepsia, diarrhea, constipation, aerophagia, meteorism	Irritability, restlessness, apprehension
Genito-urinary: frequent urination, sexual problems	Behavior to avoid certain situations
	Inhibition or psychomotor blockage Obsessions or compulsions

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Anxiety disorders as such are a group of illnesses characterized by the presence of excessive worry, fear, tension, or activation that causes significant discomfort or a clinically significant deterioration of the activity of the individual [30].

The causes of anxiety disorders are not fully understood, but biological, environmental, and psycho-social factors are involved [31,32].

The biological factors include alterations in neurobiological gabaergic, and seratonergic systems, as well as structural anomalies in the limbic system (paralimbic cortex), one of the most-affected regions of the brain. Certain physical alterations and greater frequency of usage and/or withdrawal from medicines, alcohol, drugs and/or sedatives, and other substances. Lastly, there is a certain genetic predisposition in the appearance of these disorders [33-36] .

The environmental factors include the influence of certain environmental stress agents, greater hypersensitivity, and learned response [36,37]. The psychosocial risk factors for these disorders include stressful situations, family environment, threatening life experiences, and excessive worry about common subjects. The pre-disposition factors include the influence of personality characteristics [32].

It appears that the interaction of multiple determining factors favors the appearance of these anxiety disorders [38], and comorbity with other mental disorders, such as mood disorders, is common [34,39].

4.2. Classifications

There are several universal criteria for determining whether a person's behavior can be diagnosed as an anxiety disorder. These criteria are included in the two most important mental (or psychopathological) disorder classifications:

- *DSM-IV- TR* (American Psychiatric Association, APA).
- *CIE-10* (World Health Organization, WHO).

The DSM-IV-TR lists twelve anxiety disorders, and in the CIE-10, neurotic disorders (anxiety) are grouped with stress-related and somatomorphic disorders (table 5)[40,41].

Table 5. Anxiety disorder classifications according to the DSM-IV-TR and the CIE-10: equivalence

DSM-IV-TR	CIE-1O
	Phobic anxiety disorder
Social phobia	Social phobias
Simple phobia	specific (isolated) phobias
Agoraphobia without history of panic disorder	Agoraphobia
	Other anxiety disorders
Panic disorder with agoraphobia	Panic disorder
Panic disorder without agoraphobia	

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Table 5. Anxiety disorder classifications according to the DSM-IV-TR and the CIE-10: equivalence

DSM-IV-TR	CIE-1O
	Phobic anxiety disorder
Generalized anxiety disorder	Generalized anxiety disorder
	Mixed anxiety and depressive disorder
	Other mixed anxiety disorders
	Other specified anxiety disorders
Obsessive-compulsive disorder	**Obsessive-compulsive disorder**
	Reaction to severe stress and adjustment disorders
Post-traumatic stress disorder	Post-traumatic stress disorder
Acute stress disorder	Reaction to severe stress
	Adjustment disorders
	Dissociative disorders
Anxiety disorder due to medical condition	
Substance-induced anxiety disorder	
	Somatoform disorders
Anxiety disorder not otherwise specified	**Other neurotic disorders**

The following table presents the classification of these anxiety disorders according to the **DSM-IV-TR-AP manual[30].** This manual was prepared between Primary Care and Psychiatry in order to diagnose mental disorders in PC, and all of the codes included in it are taken from the DSM-IV-TR. Table 6 includes the anxiety disorders according to the DSM-IV-TR-AP, along with the official codes of the CIE-9-MC and the CIE-10 codes.

Table 6. Anxiety disorder classification according to the DSM-IV-TR-AP

CIE-10	Disorder (according to DSM-IV-TR-AP)	CIE-9
F06.4	Anxiety disorder due to… (specify illness)	[293.84]
F10.8	Alcohol-related anxiety disorder	[291.89]
F19.8	Other sustance-related anxiety disorder	[292.89]
F40.01	Panic disorder with agoraphobia	[300.21]
F41.0	Panic disorder without agoraphobia	[300.01]
F40.1	Social phobia	[300.23]
F40.2	Specific phobia	[300.29]
F40.00	Agoraphobia without history of panic disorder	[300.22]
F93.0	Separation anxiety disorder	[309.21]
F42.8	Obsessive-compulsive disorder	[300.3]
F43.1	Post-traumatic stress disorder	[309.81]
F43.0	Acute stress disorder	[308.3]

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Table 6. Anxiety disorder classification according to the DSM-IV-TR-AP

CIE-10	Disorder (according to DSM-IV-TR-AP)	CIE-9
F41.1	Generalized anxiety disorder	[300.02]
F43.28	Adjusment disorder with anxiety	[309.24]
F41.9	Non-specific anxiety disorder	[300.00]

And lastly, the *International Primary Care Classification "CIAP-2"* from the WONCA[42]. This classification is based on three-digit alphanumeric codes, which can be expanded if necessary. The first is a letter that represents the organic system or apparatus, and covers the 17 chapters of this classification. Anxiety-related aspects would be represented under the "P-psychological problems" heading of the abbreviated CIAP-2 codes. The second and third digits are numbers, called components, which are related specifically or non-specifically with: signs or symptoms; administrative, diagnostic, preventive, or therapeutic procedures; complementary test results; referrals, tracking, or other visit motives, or illnesses and health problems. The CIAP-2 codes that correspond to anxiety are shown in the table below as components. The table also specifies the equivalence with the CIE-10 codes:

Table 7. Abbreviated CIAP-2 codes for anxiety

P. Psychological problems	
Component 1: signs and symptoms Feelings of anxiety/tension/nervousness: P01 Equivalence with the CIE-10: F41.9, R45.0	Component 7: health problems and illnesses Anxious-state/anxiety disorders: P74 Equivalence with the CIE-10: F41.0, F41.1, F41.3 to F41.9

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5. Diagnosing anxiety

This chapter will answer the following questions:

- What are the diagnostic criteria of the different anxiety disorders?
- What are the criteria for suspecting anxiety disorders?
- What studies should be done initially with adults suspected to suffer anxiety disorders in order to allow early detection?
- Are there key questions that could help Primary Care professionals to detect anxiety disorders in patient interviews?
- What are the differential diagnoses to be taken into account?

5.1. Diagnostic criteria

This section describes the diagnostic criteria with which anxiety disorders must conform as specified in the DSM-IV-TR [40]. The proposed system is the one described in the DSM-IV-TR AP [30] manual, in the form of steps, although it has been modified. The criteria of the DSM-IV-TR were taken into account in cases in which they were summarized in the DSM-IV-TR-AP:

Step 1

Consider the role of a medical illness or the consumption of substances and take into account whether the anxiety is better explained by another mental disorder:

1A. Consider the role of medical illnesses

Anxiety disorder due to a general medical condition

A. Prominent anxiety, Panic Attacks, or obsessions or compulsions predominate in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (e.g., Adjustment Disorder With Anxiety in which the stressor is a serious general medical condition).

D. The disturbance does not occur exclusively during the course of a Delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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1B. If the subject takes abused substances or medication, consider the following:

Substance-induced anxiety disorder (including medication)

A. Prominent anxiety, Panic Attacks, or obsessions or compulsions predominate in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

(1) the symptoms in Criterion A developed during, or within 1 month of, Substance Intoxication or Withdrawal.

(2) medication use is etiologically related to the disturbance.

C. The disturbance is not better accounted for by an Anxiety Disorder that is not substance induced. Evidence that the symptoms are better accounted for by an Anxiety Disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence suggesting the existence of an independent non-substance-induced Anxiety Disorder (e.g., a history of recurrent non-substance-related episodes)

D. The disturbance does not occur exclusively during the course of a Delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

1C. Consider the role of other mental disorders that could explain the anxiety symptoms better

Additional comments:

- Differential diagnosis:

  In the case of a patient that presents a differential diagnosis with an anxiety disorder, systemic illnesses should be reasonably ruled out. To do this, you should take into account the physical symptoms that predominate, the knowledge of the prior medical and psychological history of both the patient and the patient's family and the illnesses that generate anxiety disorders, as well as the probability of the ones that may be affecting the patient. Do not forget high capacity of toxins such as caffeine, cannabis, or cocaine and other synthetic drugs to induce anxiety attacks and panic in predisposed subjects. It is also necessary to consider the importance of alcohol for many of the people who suffer anxiety (especially generalized anxiety, panic disorder, and social phobia) since it is used as a tranquilizer to relieve the anxiety symptoms. Based on all of these factors, determine the additional tests that should be carried out, depending on the level of suspicion and the immediacy with which the tests must be carried out, depending on the symptoms and the evaluation.

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- Medical comorbidity in anxiety disorders:

  A wide range of medical illnesses can produce symptoms of anxiety, although this field – comorbidity – is likely to change because an increasing number of somatic disorders are being described in patients affected by pathological anxiety. The current differentiation between primary disorders or those "due" to a medical illness will give way to those that are "associated with somatic pathology". As is the case of depression or bipolar disorder, the coexistence of auto-immune thyroid pathology, asthma, migraines, etc. progressively highlights the probability that these are different manifestations of a single systemic source [43]. In the case of patients with diagnosed anxiety disorders, several studies have shown a higher prevalence of gastrointestinal, genitourinary, osteomuscular, thyroid, and allergic disorders, as well as migraines, cardipathy, and hyperlaxitude in joints, in comparison with patients without anxiety disorders [44-47].

Step 2

Panic attack

Panic attacks are defined as follows:

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes.

Cardiopulmonary symptoms:

1. chest pain or discomfort.
2. sensations of shortness of breath or smothering.
3. palpitations, pounding heart, or accelerated heart rate.

Autonomic symptoms:

4. Sweating.
5. chills or hot flushes.

Gastrointestinal symptoms:

6. Feeling of choking.
7. Nausea or abdominal distress.

Neurological symptoms:

8. trembling or shaking.
9. paresthesias (numbness or tingling sensations).
10. feeling dizzy, unsteady, lightheaded, or faint.

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Psychiatric symptoms:

11. derealization (feelings of unreality) or depersonalization (being detached from oneself).
12. Fear of losing control or going crazy.
13. Fear of dying.

2A. If panic attacks are unexpected (they occur "out of the blue" and are not related to a situational trigger) and they are clinically significant, consider the following:

Panic disorder with agoraphobia

A. Both (1) and (2):

(1) recurrent unexpected Panic Attacks.

(2) at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:

(a) persistent concern about having additional attacks.

(b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy").

(c) A significant change in behavior related to the attacks.

B. The presence of agoraphobia:

(1) Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed Panic Attack or panic-like symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd or standing in a line; being on a bridge; and traveling in a bus, train, or automobile.

Note: Consider the diagnosis of Specific Phobia if the avoidance is limited to one or only a few specific situations, or Social Phobia if the avoidance is limited to social situations.

(2) The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a Panic Attack or panic-like symptoms, or require the presence of a companion.

(3) The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as Social Phobia (e.g., avoidance limited to social situations because of fear of embarrassment), Specific Phobia (e.g., avoidance limited to a single situation like elevators), Obsessive-Compulsive Disorder (e.g., avoidance of dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., avoidance of stimuli associated with a severe stressor), or Separation Anxiety Disorder (e.g., avoidance of leaving home or relatives).

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C. The Panic Attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

D. The Panic Attacks are not better accounted for by another mental disorder, such as Social Phobia (e.g., occurring on exposure to feared social situations), Specific Phobia (e.g., on exposure to a specific phobic situation), Obsessive-Compulsive Disorder (e.g., on exposure to dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., in response to stimuli associated with a severe stressor), or Separation Anxiety Disorder (e.g., in response to being away from home or close relatives).

OR

Panic disorder without agoraphobia

A. Criterion A of panic disorder with agoraphobia is fulfilled.

B. Absence of agoraphobia.

C and D. Same as in the case of panic disorder with agoraphobia.

2B. If the panic attack is related to a situational trigger associated with another mental disorder, consider the following:

Panic attacks that occur in the context of other anxiety disorders (e.g. social phobia, specific phobia, post-traumatic stress disorder, obsessive-compulsive disorder).

Step 3

If the symptom is fear, avoidance, or anxious anticipation of one or more specific situations, consider 3A, 3B, and 3C:

3A. If the symptoms are related to social situations or actions in which the individual is exposed to people from outside the family circle or the possible evaluation by others, consider:

Social phobia

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing.

Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.

B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed Panic Attack. Note: In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.

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C. The person recognizes that the fear is excessive or unreasonable. Note: In children, this feature may be absent.

D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18 years, the duration is at least 6 months.

G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., Panic Disorder With or Without Agoraphobia, Separation Anxiety Disorder, Body Dysmorphic Disorder, a Pervasive Developmental Disorder, or Schizoid Personality Disorder).

H. If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g., the fear is not of Stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in Anorexia Nervosa or Bulimia Nervosa.

3B. If the symptoms include the avoidance of specific situations or objects, consider the following:

Specific phobia

A. Marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

B. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally bound or situationally predisposed Panic Attack.

Note: In children, the anxiety may be expressed by crying, tantrums, freezing, or clinging.

C. The person recognizes that the fear is excessive or unreasonable. Note: In children, this feature may be absent.

D. The phobic situation(s) is avoided or else is endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18 years, the duration is at least 6 months.

G. The anxiety, Panic Attacks, or phobic avoidance associated with the specific object or situation are not better accounted for by another mental disorder, such as Obsessive-Compulsive Disorder (e.g., fear of dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., avoidance of stimuli associated with a severe

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stressor), Separation Anxiety Disorder (e.g., avoidance of school), Social Phobia (e.g., avoidance of social situations because of fear of embarrassment), Panic Disorder with Agoraphobia, or Agoraphobia Without History of Panic Disorder.

3C. If the anxiety or avoidance is related to situations in which escape may be difficult or situations in which there is no help available if a panic attack occurs and there is no history of panic attacks, consider the following:

Panic disorder with agoraphobia

3D. If the symptom is related to a situation in which escape may be difficult or situations in which there is no help available if a panic attack occurs and there is no history of panic attacks, consider the following:

Agoraphobia without history of panic disorder

A. The presence of Agoraphobia related to fear of developing panic-like symptoms (e.g., dizziness or diarrhea).

B. Criteria have never been met for Panic Disorder.

C. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

D. If an associated general medical condition is present, the fear described in Criterion A is clearly in excess of that usually associated with the condition.

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Step 4

4. If the apprehension or anxiety are related to persistent thoughts (obsessions) and/or rituals or recurrent mental acts (compulsions), consider the following:

Obsessive-compulsive disorder

A. Either obsessions or compulsions: **Obsessions** as defined by (1), (2), (3), and (4):

(1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress.

(2) the thoughts, impulses, or images are not simply excessive worries about real-life problems.

(3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action.

(4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion).

Compulsions as defined by (1) and (2):

(1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.

(2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. Note: This does not apply to children.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorders; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use

* The multi-axis classification of the DSM-IV-TR [40] includes five axes:
Axis I Clinical disorders. Other conditions that may be a focus of clinical attention
Axis II Personality disorders. Mental retardation
Axis III General medical conditions
Axis IV Psychosocial and environmental problems
Axis V Global assessment of functioning

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Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder)

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Step 5

If the symptoms are related to reexperiencing of highly traumatic events, consider 5A and 5B:

5A. If the symptoms are related to the reexperience of highly traumatic events and the symptoms last less than 4 weeks, consider:

Post-traumatic stress disorder

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.

(2) the person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.

(2) recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.

(3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note: In young children, trauma-specific reenactment may occur.

(4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

(5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

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C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, feelings, or conversations associated with the trauma.

(2) efforts to avoid activities, places, or people that arouse recollections of the trauma.

(3) inability to recall an important aspect of the trauma.

(4) markedly diminished interest or participation in significant activities.

(5) feeling of detachment or estrangement from others.

(6) restricted range of affect (e.g., unable to have loving feelings).

(7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(1) difficulty falling or staying asleep.

(2) irritability or outbursts of anger.

(3) difficulty concentrating.

(4) hypervigilance.

(5) exaggerated startle response.

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

5B. If the symptoms persist for at least 2 weeks but not more than 4 weeks, consider:

Acute stress disorder

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.

(2) the person's response involved intense fear, helplessness, or horror.

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B. Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:

(1) a subjective sense of numbing, detachment, or absence of emotional responsiveness.

(2) a reduction in awareness of his or her surroundings (e.g., "being in a daze").

(3) Derealization.

(4) Depersonalization.

(5) dissociative amnesia (i.e., inability to recall an important aspect of the trauma).

C. The traumatic event is persistently reexperienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event.

D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people).

E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness).

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or impairs the individual's ability to pursue some necessary task, such as obtaining necessary assistance or mobilizing personal resources by telling family members about the traumatic experience.

G. The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event.

H. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition, is not better accounted for by Brief Psychotic Disorder, and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

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Step 6

If the symptoms of intense anxiety and worry are related to a variety of events or situations, consider the following:

Generalized anxiety disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). Note: Only one item is required in children:

(1) restlessness or feeling keyed up or on edge.

(2) being easily fatigued.

(3) difficulty concentrating or mind going blank.

(4) Irritability.

(5) muscle tension.

(6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep).

D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a Panic Attack (as in Panic Disorder), being embarrassed in public (as in Social Phobia), being contaminated (as in Obsessive-Compulsive Disorder), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in Anorexia Nervosa), having multiple physical complaints (as in Somatization Disorder), or having a serious illness (as in Hypochondriasis), and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder.

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Step 7

If the symptoms appear in response to specific psycho-social stress, consider:

Adjustment Disorder with anxiety

A. The development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s).

B. These symptoms or behaviors are clinically significant as evidenced by either of the following:

(1) marked distress that is in excess of what would be expected from exposure to the stressor.

(2) significant impairment in social or occupational (academic) functioning.

C. The stress-related disturbance does not meet the criteria for another specific Axis I disorder and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

D. The symptoms do not represent Bereavement.

E. Once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 months.

Step 8

If the anxiety is clinically significant and the criteria are not fulfilled for any of the specific disorders described above, consider:

Non-specific anxiety disorder

This includes disorders with prominent symptoms of anxiety or phobic avoidance that do no fulfill the diagnostic criteria for any of the specific disorders described above. The following are several examples:

(1) *Mixed anxiety-depressive disorder:* this is a persistent or recurring dysphoric mood state that lasts at least 1 month and is accompanied for at least 1 month by other anxious and depressive symptoms (e.g. difficulty concentrating or having your mind blank, sleep disorders, fatigue or lack of energy, irritability, worry, crying easily, hypervigilance, anticipation of danger, desperation, and low self-esteem or feelings of uselessness). These symptoms can cause deterioration of the individual's social or work relations or other important areas of their activities.

(2) Clinically significant social phobic symptoms that are related to the social impact of having a general medical condition or mental disorder (e.g., Parkinson's disease, dermatological conditions, stuttering, anorexia nervosa, body dysmorphic disorder.

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(3) Situations in which the alteration is serious enough to require a diagnosis of anxiety disorder, even though the individual does not present a sufficient number of symptoms to fulfill all of the criteria for a specific anxiety disorder.

(4) Situations in which the clinical evidence confirms the presence of an anxiety disorder, but it is impossible to determine whether it is a primary disorder, due to medical illness, or substance-induced.

Cultural aspects related to anxiety

The immigrant population in Spain is continually increasing. This population presents some specific clinical characteristics in the different psychiatric disorders, with symptoms that are dependent on their individual cultures. In the case of anxiety disorders, many of these disorders are diagnosed as psychosis due to the presence of hallucinations and delirious intense fears. Likewise, panic attacks can be triggered by fear of magic or witchcraft. There are also syndromes connected to culture, which have now been described in our context, that are related to anxiety disorders, such "Koro" and "nervous breakdown" [48-52].

5.2. Semi-structured interview

To achieve an overall understanding of the patient and to be able to establish a diagnosis of anxiety disorders, the ideal instrument is the clinical interview [53,54]. The interview is used to establish or update the basis of the relationship and gathers or fails to gather the information needed to guideline the diagnosis and the decision as to the strategies to be followed.

By attempting to systematize the technique, between a guided interview and an open interview, the *semi-structured* interview combines both types, adapting to the characteristics of the doctor-patient encounter that takes place in the Primary Care environment (it combines time management, bio-psychosocial approach, and focuses on the patient as the expert on him or herself. It begins with more open questions (the content of which is partially pre-determined by the healthcare professional), supports the patient's narrative, and later directs the encounter with more specific or closed questions that avoid leaving unanswered questions that are essential to identify and treat the problem. The different parts of a semi-structured interview are described in the table below [55-58].

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Table 8. Phases of the semi-structured interview[59-61]

Preliminary phase	Exploratory phase	Resolution phase	Final phase
• Empathetic reception • Determine the reason for the visit • Avoid the "and while I'm here", limiting the reasons for the visit	• Obtain basic specific information: - What the symptoms are like - Location - Intensity - Chronology and evolution • Gather specific additional information: - Presence of organic or yatrogenic pathology - Trigger factors: changes, grieving… - Social-family environment - Personal history: manic episodes, prior episodes of depression - Situations that improve or worsen • Exploration of the psychosocial sphere: - Beliefs and expectations - Content of thought - Affectivity - Personality	• Synthesis and listing of the problem(s) • Inform the patient regarding the nature of the problem • Verify that the patient has understood the explanations • Involve the patient in the preparation of a diagnostic-therapeutic plan: - Agreements - Negotiation	• Taking precautions • Final agreement • Goodbye

In the exploratory phase, normally the Primary Care professional has already gathered much of the supplementary information and the information on the psycho-social environment of a patient whom the professional and the rest of the team already know, which facilitates the process. In the final phase of the interview, the *final agreement* should be emphasized, as the reconversion of the ideas and agreements reached [59-61].

5.3. Use of scales

The confirmation of the aforementioned under-diagnosis of anxiety has given rise to a large number of structured instruments or scales that try to detect "potential cases" of illness.

Many of the scales are intended to serve as filtering instruments, and with all of them, once the potential case has been detected, the corresponding diagnostic procedure can then be applied.

The scales in and of themselves do not generate diagnoses, but rather make it possible to select people with high scores who are suspected of suffering a mental pathology, which justifies the later execution of a more in-depth study [62].

These measurement instruments also serve to complete a proper evaluation, since they reinforce the diagnostic judgment prepared after the clinical interview and the psychopathological exploration.

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All of these instruments have the limitations of detecting false positives and negatives, since they all have a sensitivity and specificity that is lower than 100%. It is therefore neither feasible nor advisable to use the scales routinely in Primary Care for clinical purposes, and under no circumstances should they substitute the clinical interview, even though they are useful as a guideline for the interview and to support the clinical judgment, and they have also become essential tools in clinical research, and also serve to verify the effect that the different therapeutic interventions have on the evolution of the illness [62,63].

Since the time available to evaluate patients in Primary Care offices is limited, the instruments to be used should be easy to use and interpret. The following sections describe several of the scales related to anxiety [59,64,65].

Goldberg Anxiety and Depression Scale (GADS)[66]

This scale was conceived to allow the detection of the two most frequent psychopathological disorders in Primary Care. It is a simple instrument that is short and easy to use, and is suitable for administration by Primary Care doctors. It can be used as a guideline for the interview, as well as an indicator of the prevalence, gravity, and evolution of these disorders. The Spanish version has demonstrated its reliability and validity in Primary Care use and has adequate sensitivity (83.1%), specificity (81.8%) and positive predictive value (95.3%).

Hospital, Anxiety, and Depression (HAD)[67]

A scale of 14 items designed to evaluate anxiety and depression in non-psychiatric hospital outpatient services. This is a state measurement that contains two scales, one for anxiety and the other for depression. One of the main virtues is the suppression of somatic symptoms so that it is possible to independently evaluate the underlying somatic illness. This is a useful instrument validated in our system and is especially interesting and useful in the context of Primary Care [68].

HARS-Hamilton Anxiety Rating Scale (Chamorro)

This scale evaluates anxiety intensity. It consists of 14 items that evaluate mental, physical, and somatic aspects of anxiety. On item will evaluate depressed mood. It is a externally-applied scale. There is a version adapted to Spanish by Carrobles and cols. (1986). Depending on the type of symptom, it will be measured in terms of seriousness, duration, and dysfunction, from lower to higher.

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Clinical Anxiety Scale (CAS) and Physician Questionnaire (PQ)

These are externally-administered scales that evaluate the gravity of the symptoms in diagnosed anxiety patients. The evaluation lapse of the CAS covers the last two days, with the PQ covering the last week. The CAS was designed based on the content areas present in the HARS (Hamilton Anxiety Rating Scale) and consists of 7 items. It is specially designed to evaluate psychological symptomology and is influenced very little by somatic manifestations of anxiety. The PQ includes 14 items and evaluates neurotic symptomology and response to treatment. The symptomology covered includes the symptoms that are most familiar to and most commonly observed by general physicians. This test includes a group of emotional symptoms, another group of somatic symptoms, an overall rating, and 1 independent item that evaluates the general gravity of the anxiety disorder. Because they are brief, both scales may be useful in evaluating anxiety disorders in outpatient care, either in hospitals or in Primary Care facilities.

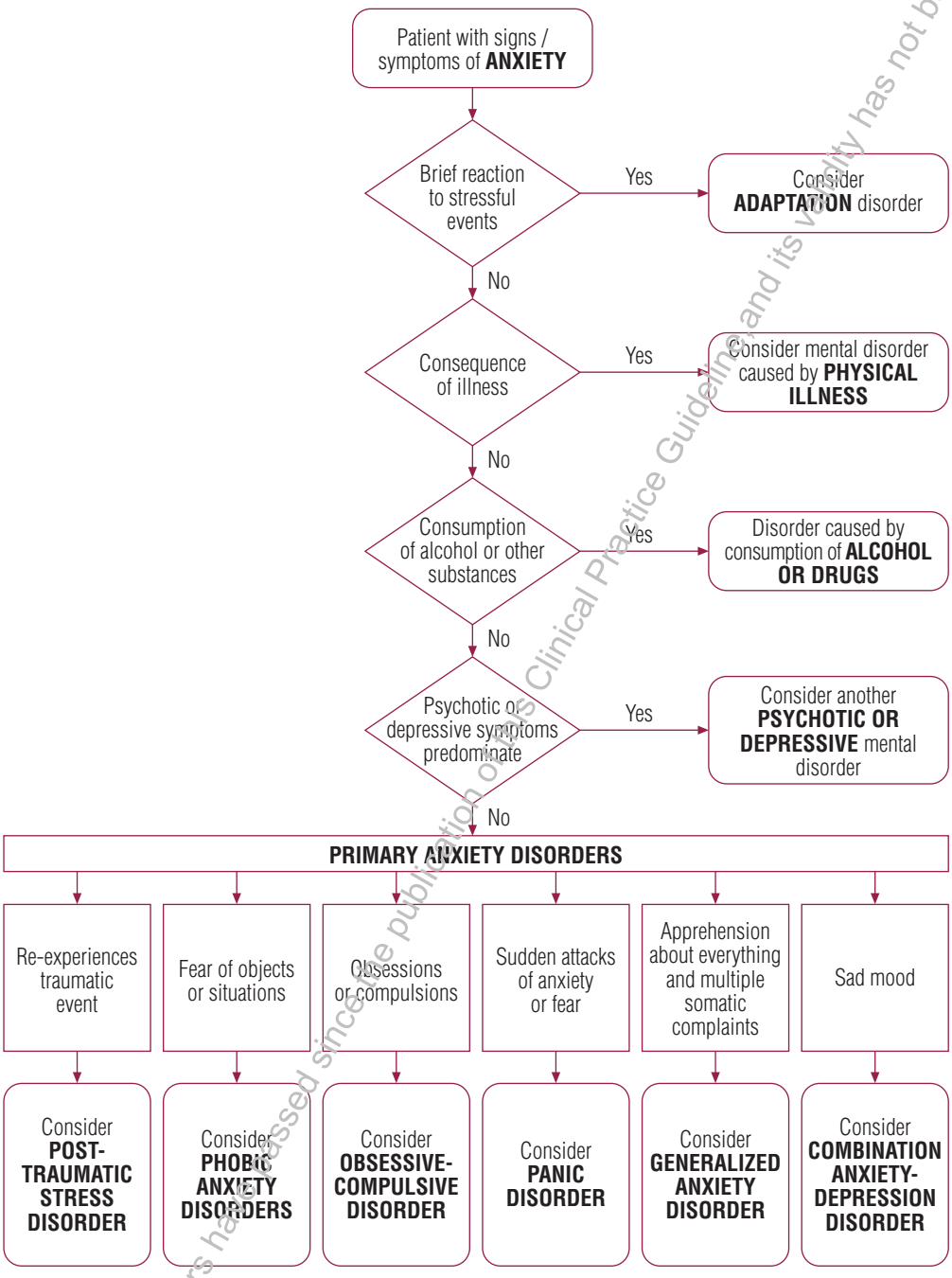
The appendices include two scales, one self-administered (HAD) and the other externally-administered (GADS) (Appendix 2), since they are easy to handle and interpret within the scope of PC, and are useful to provide key questions to guideline the clinical interview and to evaluate the changes achieved with the different interventions, but not to filter the population. These scales have not been validated with the immigrant population, so it is possible that their sensitivity/specificity, as well as their clinical utility for these patients will be more limited [48].

Another appendix also includes a series of key questions to be asked during the interview with the patient to assist healthcare professionals to detect anxiety disorders, specifically Generalized Anxiety Disorder and Panic Disorder [70] (Appendix 3).

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5.4. Diagnostic algorithm

The following diagnostic algorithm provides some initial guidelines when faced with a patient with anxiety symptoms:



Source: Modified from Pascual Pascual P., Villena Ferrer A., Morena Rayo S., Téllez Lapeira J.M., *El paciente ansioso.* Internet. Fisterra.com; 2005.

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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 health[71], for the purpose of causing existing symptoms to disappear or change, attenuate or change behavior and promote growth and development of a positive personality[72].

Qualitative study

The published results of studies that ask people who visit Primary Care indicate that they either positively accept the psychological interventions[22], or they prefer psychological therapy to pharmacological treatments as a way of treating mental health disorders[73].

A clinical research study done in Spain emphasized that the principles that must be included in a "support" relationship offered by the Primary Care doctor[74] 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 instrument[75].

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, dissents, 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.

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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 psychotherapies[78]

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.

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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 automatically[79].

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 treatment[83-85].

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 account[80].

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 monitoring[82].

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 GAD[86]. 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 therapy[86].

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

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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 disorder[86].

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 diagnosis[89].

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 effectiveness[88].

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 RCTSs[92], 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-

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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.

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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 *depression*[70,80-82,86].
1++	The CBT studied includes cognitive restructuring, exposure, relaxation and systematic desensitization, with an average of eight months of *treatment*[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].

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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 treatment[79].

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 treatment[95] or during follow-up[96]; 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-centreed therapy, to be therapies with probable beneficial effects for the treatment of PD[98].

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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 **PD**[80]. 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 studies[99-101], 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 panic[82].

Meta-analysis 1++

There is a meta-analysis[102] 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 in to 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 r educe 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 treatment[98]. 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

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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 specialists[92].

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 therapy[106].

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.

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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 needed[107].

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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 *in vivo* 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 in vivo 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.

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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 received[108].

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-medication[109-112].

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 crises[61]. 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: • 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.

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

√	The following psychological techniques are recommended in PC to control symptoms related to panic attacks: • 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.
√	The family should be informed regarding the type of actions to help in resolving any new attacks.

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 applicability[77], 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:

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Table 9*. Behavioral Techniques in Primary Care[59,113]

Expert opinions 4	Relaxation techniques: to achieve a state of hypoactivation that counteracts and helps control anxiety • Training in progressive relaxation • Training in breathing control Exposure techniques: exposure to stimuli that cause anxiety, in order to predict and reduce adaptive responses • Systematic desensitization • Gradual exposure in vivo Self-control techniques: these teach the patient the principles that govern the undesired behavior • Self-observation • Self-reinforcement or self-punishment • Control of stimuli Training in social skills: after analyzing the problem behavior and retraining it.

*Modified García-Vera in Vázquez-Barquero[59].

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	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. 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. Cognitive distraction and thought stopping: focus attention on neutral, non-threatening stimuli (count streetlights, shoe store display windows, etc.). 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. 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.

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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 themselves[78].

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.

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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	The following common characteristics have been found in the brief interventions carried out in PC, individually or in groups, to obtain greater effectiveness[77]: • 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	The following techniques are recommended in PC to reduce symptoms related to panic attacks: • 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. • *Counseling:* 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)

√	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.
√	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.

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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 GAD[122]. 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].

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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 effectives in comparison with other anti-depressants[126-128].

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 fetus[131-136].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and it has not been reviewed

* 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].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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 obtained[70].

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 GAD[70].

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

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 fetus[142-144]. 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].

More than 5 years have passed since the publication of this clinical practice guideline and its validity has not been reviewed

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 fro 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-HT1A 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, hydroxicine, 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.

Pregabaline

CPG (SR and RCTS) 1+ RCTS 1+

Pregabaline in 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].

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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 zyprasidone 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].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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].
Pregabaline	
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 zyprasidone 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 pregabline, 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.

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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 complications[162]. 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 disorder[163].

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+

The USFDA (Food and Drug Administration) has issued several warnings in regard to the use of SSRIs and increased risk of self-inflicted injury, suicide, and hyponatremia[129]. 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 monotherapy[131-136] .

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 PD70.80-82.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

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].

More than 5 years have passed since the publication of the Clinical Practice Guideline and its validity has not been reviewed

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 fenelzine appear to be effective in the treatment of PD. Trials on the effectiveness of MARI (moclobemide) have not shown such clear results[70,82].

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

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.

Note[142]:

- 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 anxiety[166]. The slow--release formula appears to have good initial speed of effect, with the advantage of longer duration of its therapeutic action[170]. The short-term use of clonazepam at the start of treatment, along with SSRIs can result in faster response[61]. 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].

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

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+

SExisting 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]. 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]. 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.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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 risp eridone, added to anti-depressive treatment, may have some benefit in the treatment of refractory PD[70,155,172] .

CPG (RCTS) 1+/1-

Other[70]

- Pindolol: beta-blocker and antagonist of the 1A seratonin ergic 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), propanolol (beta-blocker) and carbamazepine (anti-convulsive) have not been shown to be effective in the treatment of PD, so their use is not recommended.

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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, propanolol, 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 bupriopion, 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, propanolol, 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 placebo[173].

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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].

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 review[174] 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, azaspirones, 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 between 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, azaspirones, 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]

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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.

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 direct[176] 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.

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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 BCT[177-179].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

SR of RCTS 1++

Later, a systematic review from the Cochrane[180] 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 anti-depressants alone should not be recommended as a first treatment option when other more appropriate therapies are available[180].

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 RCTS[181] 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.

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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 RCTS[183] 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 limited[180].

RCTS 1+
pre-post-estudy 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].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its study has not been reviewed

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.

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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 PD[187]. 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 used[187].

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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 months[188].

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 Care[189]. 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 properly[190].

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 patient[191].

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 incapacitation[192].

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 interventions[190].

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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 psychologist[61], 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 RCTSs 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 effects[198].

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 required[200].

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 GAD[201]. 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 effectiveness[198]; its use may be as effective as buspirone or opipramol for acute treatment of *GAD*[202] and significantly improves sleep disorders associated with anxiety disorders[203].

RCTS 1+, Series of cases 3, Legal regulations

It continues to be the object of controversy regarding its safety of usage[204]. There are RCTS that focus more on the side effects associated with hepatic toxicity; the FDA has issued warnings in this regard[206], , 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 toxicity[207]. 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 toxicity[198]. 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 acceptable[198].

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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 disorders[208]. 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 functions[211].

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

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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 better[212].

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 anxiety[213].

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.

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7. Information/communication with the patient[80.82]

This chapter will answer the following questions:

- What is the basic information that should be given to patients with anxiety disorders?
- What is the basic information that should be given to the families of patients with anxiety disorders?
- What is the best way to inform patients of their disorders?

CPG (Expert opinions) 4

Patient information forms part of the integrated treatment of generalized anxiety disorders, panic disorder, and/or panic attack, at the Primary Care Level.

Providing the patient, and when appropriate, the family, information based on the evidence, nature, and origin of their symptoms, the treatment options, and the possibilities of treating their anxiety disorder, facilitates shared decision making. This involvement of patients in the decision-making process, as well as an interactions style based on empathy and understanding, increases satisfaction with the visit – increasing trust – and improves the clinical results. Shared decision-making begins with the diagnostic process, and is maintained in all of the phases of treatment. Common language, and if appropriate, written material that is also understandable for the patient should be used to facilitate this[80.82].

In regard to the possible treatment options, the patient preferences and experiences with other treatments must be taken into account, guided by the most common concerns in patients with anxiety disorders, especially those related to medication, side effects, and fears of possible addiction.

Proper handling of these patients in the doctor's office requires the evaluation of the possibility of family support, taking into account the available social resources, and suggesting the lifestyle changes that would be best suited for the patients.

The information aimed at the patient/family is included in Appendix 4.

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Evidence on information/communication with patients with Generalized Anxiety Disorder (GAD), Panic Disorder (PD) and/or Panic Attack

4	Patient information forms part of the integrated treatment of generalized anxiety disorders, panic disorder, and/or panic attack, at the Primary Care Level[80.82].
4	Providing the patient, and when appropriate, the family, information based on the evidence, nature, and origin of their symptoms, the treatment options, and the possibilities of treating their anxiety disorder, facilitates shared decision making[80.82].
4	This involvement of patients in the decision-making process, as well as an interactions style based on empathy and understanding, increases satisfaction with the visit – increasing trust – and improves the clinical results[80.82].
4	Shared decision-making begins with the diagnostic process, and is maintained in all of the phases of treatment[80.82].

Recommendations regarding information/communication with patients with Generalized Anxiety Disorder (GAD), Panic Disorder (PD) and/or Panic Attack

√	Information for the patient should form part of the integrated treatment of anxiety disorders at the Primary Care level.
D	The patient, and when appropriate, the family, should be given information based on the evidence regarding their symptoms, treatment options, and the possibilities of treating their disorders, taking patient preferences into account to facilitate joint decision-making.
D	A contact style based on empathy and understanding is recommended to improve patient satisfaction.
D	The possibility of family support should be assessed, taking into account the available social resources, and suggesting the most appropriate changes in lifestyle.

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8. Diagnostic and therapeutic strategies

This chapter will answer the following questions:

- What are the steps to be followed in response to an anxiety disorder (GAD, PD, and panic attack)?
- What are the criteria for referral from Primary Care to Mental Health?

The answers to these questions are included in the following treatment algorithms presented in the following pages:

- Treatment of Generalized Anxiety Disorder

  Treatment algorithm for Generalized Anxiety Disorder (GAD)

- Treatment of Panic Disorder

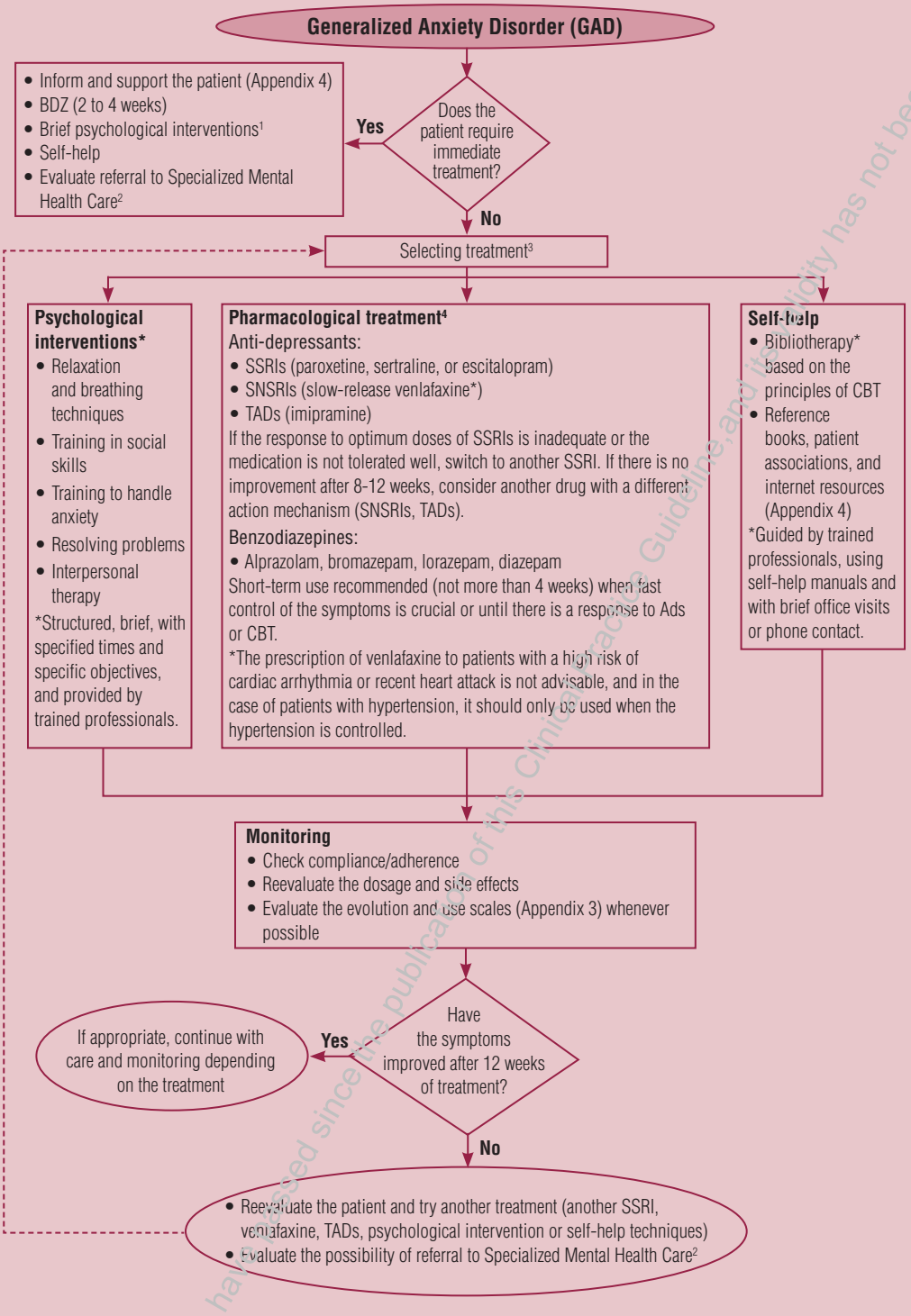
  Treatment algorithm for Panic Disorder (PD)

- Treatment of Panic Attack

  Treatment algorithm for Panic Attack (see the following page)

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8.1. Generalized Anxiety Disorder (GAD)



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1. Brief psychological interventions

Done by trained professionals:
- Relaxation and breathing
- Self-control
- Training in social skills
- Training to handle anxiety

2. Referral criteria

- Difficult or uncertain diagnosis (non-specific physical symptoms, somatizations, etc.)
- Psychiatric or organic comorbidity (major depression, alcohol dependence and/or substance abuse)
- Suicidal tendencies (urgent referral)
- In case of persistent elevated anxiety for more than 12 weeks of pharmacological treatment and/or psychotherapy support
- Highly incapacitating symptoms (social and/or work adaptation)

3. Treatment selection

- Evaluate the severity of the symptoms and criteria for referral to Specialized Mental Health Care
- Inform the patient regarding therapeutic objectives and options depending on the available resources
- Evaluate the patient's preferences and beliefs/expectations regarding the treatment

4. Pharmacological treatment

Consider the following before prescribing:
- Age
- Previous treatment
- Risk of autolytic attempts or occasional overdose
- Tolerance
- Possible interactions with other medications
- Possible pregnancy
- Patient's preference

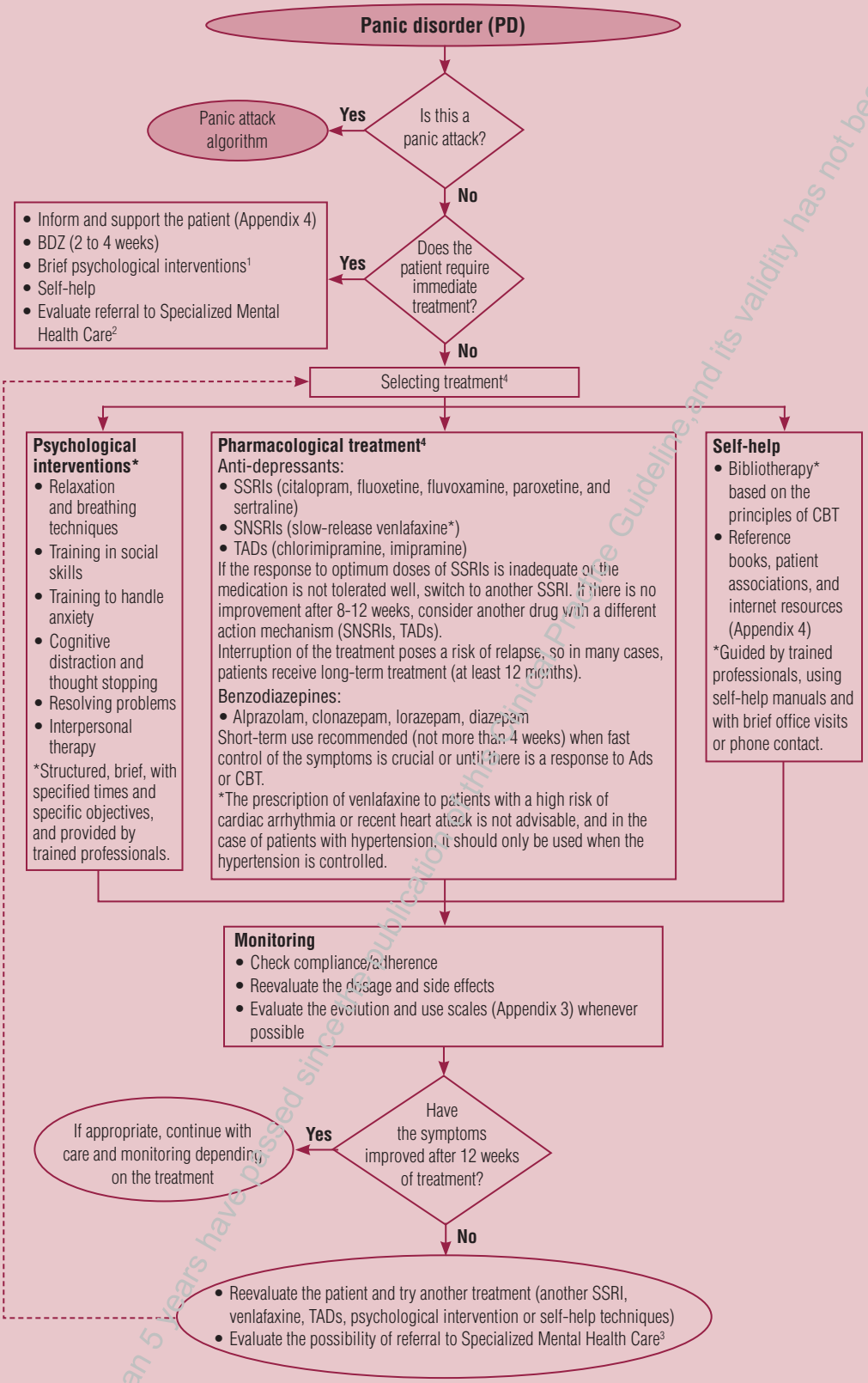
Inform the patient regarding the following:
- Possible side effects*
- Possible withdrawal symptoms after interruption of treatment
- Non-immediacy of the effect
- Duration
- Need for compliance

Make written information available to the patient (Appendix 4).

*To reduce side effects, begin with a lower dosage and increase until the satisfactory therapeutic dosage is reached.

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8.2. Panic Disorder (PD)



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1. Diagnostic criteria for panic attack (DSM-IV-TR-AP)

Temporary or isolated appearance of intense discomfort or fear, accompanies by four (or more) of the following symptoms, which appear suddenly and achieve their maximum intensity within the first 10 minutes:

1. Chest discomfort or tightness
2. Feeling of suffocation or lack of breath
3. Palpitations, heart pounding, or elevation of heart rate
4. Sweating
5. Shivering or suffocation
6. Feeling of choking
7. Nausea or abdominal discomfort
8. Shaking or trembling
9. Paresthesia (feeling of numbness or tingling)
10. Instability, dizziness, or fainting
11. Derealization (feeling of unreality) or depersonalization (being separated from one's self)
12. Fear of losing control or going crazy
13. Fear of dying

2. Brief psychological interventions

Done by trained professionals:

- Relaxation and breathing
- Self-control
- Training in social skills
- Training in the handling of anxiety symptoms

3. Referral criteria

- Difficult or questionable diagnosis
- Organic or psychiatric comorbidity (major depression, alcohol dependency and/or substance abuse)
- Suicidal tendencies (urgent referral)
- If intense anxiety persists for more than 12 weeks of pharmacological treatment and/or support psychotherapy
- Highly incapacitating symptoms (social and/or work adaptation)

4. Selecting treatment

- Evaluate the seriousness of the symptoms and criteria for referral to Specialized Mental Health Care[3]
- Inform the patient regarding the options and therapeutic objectives depending on the available resources
- Evaluate the patient's preferences and beliefs/expectations regarding the treatment

5. Pharmacological treatment

Consider the following before prescribing:

- Age
- Previous treatment
- Risk of autolytic attempts or occasional overdose
- Tolerance
- Possible interactions with other medications
- Possible pregnancy
- Patient's preference

Inform the patient regarding the following:

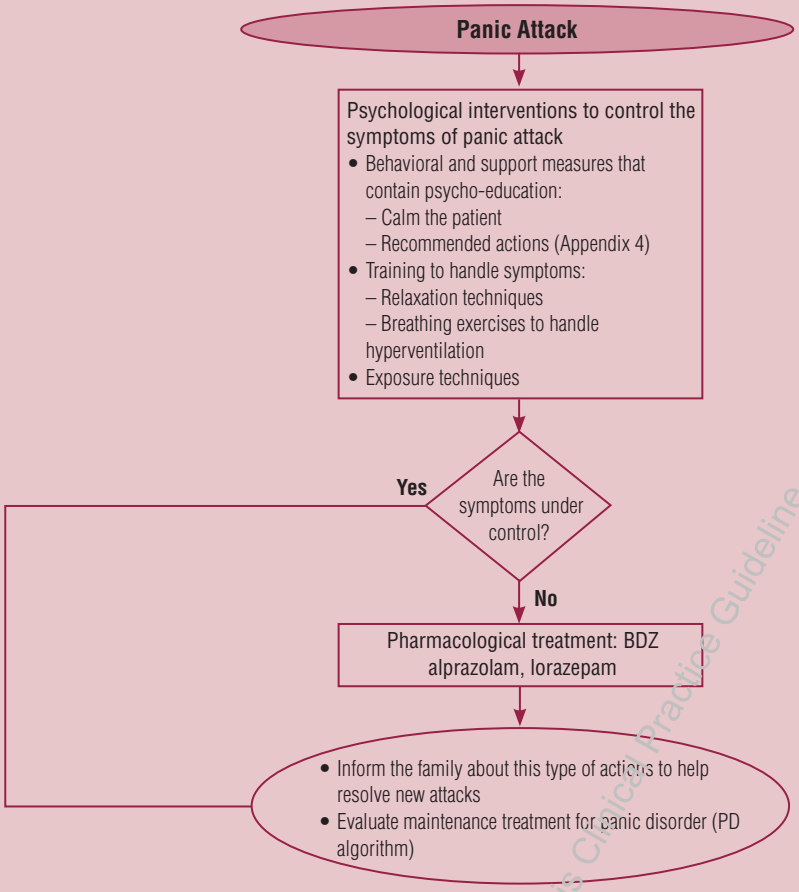
- Possible side effects*
- Possible withdrawal symptoms after interruption of treatment
- Non-immediacy of the effect
- Duration
- Need for compliance

Make written information available to the patient (Appendix 4).

*To reduce side effects, begin with a lower dosage and increase until the satisfactory therapeutic dosage is reached.

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8.3. Panic Attack



1. Diagnostic criteria for panic attack (DSM-IV-TR-AP)

Temporary or isolated appearance of intense discomfort or fear, accompanies by four (or more) of the following symptoms, which appear suddenly and achieve their maximum intensity within the first 10 minutes:

1. Chest discomfort or tightness
2. Feeling of suffocation or lack of breath
3. Palpitations, heart pounding, or elevation of heart rate
4. Sweating
5. Shivering or suffocation
6. Feeling of choking
7. Nausea or abdominal discomfort
8. Shaking or trembling
9. Paresthesia (feeling of numbness or tingling)
10. Instability, dizziness, or fainting
11. Derealization (feeling of unreality) or depersonalization (being separated from one's self)
12. Fear of losing control or going crazy
13. Fear of dying

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9. Dissemination and implementation

This chapter will answer the following questions:

- What is the strategy to circulate and implement the guideline?
- What are the indicators for tracking the key recommendations?

9.1. Dissemination and implementation strategies

Clinical practice guidelines are useful for improving the quality of care and the results in the patients. The challenge today is to convince the professionals to follow them. For this reason, an implementation strategy aimed at breaking down the barriers that exist in the environment in which they will be applied is essential.

The plan to implement the guideline on the treatment of patients with anxiety disorders in Primary Care includes the following actions:

- Presentation of the guideline by healthcare authorities to the communication media.
- Presentation of the guideline to the directorates and sub-directorates of Primary Care and Specialized Care of the different Regional Healthcare Services.
- Institutional presentation of the guideline in collaboration with the Quality Agency of the Ministry of Healthcare and Consumption to the different scientific and professional associations involved.
- All of the presentations will highlight the materials prepared for patients in order to encourage distribution among all of the healthcare professionals, and in turn among the patients with this health problem.
- Effective distribution aimed at the professional groups involved (Primary Care doctors, nurses, and social workers, Specialized Mental Health psychiatrists, psychologists, and nurses) to facilitate Dissemination.
- Interactive presentation of the guideline in healthcare centers by local opinion leaders.
- Distribution of the guideline in electronic format through the websites of the Ministry of Healthcare and Consumers Affairs, GUIASALUD, the UETS, and the organizations involved in the project.
- Publication of the guideline in medical journals.
- Establishment of criteria for good care of anxiety patients in the program and clinical management contracts, as specified in the guideline.

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- Evaluation of the effectiveness of the implementation, establishing systems to support clinical decisions, integrating the guideline and the selected indicators into the computer program used in Primary Care.

9.2. Proposed indicators

The authors of this CPG have designed a series of indicators that should be able to be measured through the Primary Care information system, for the purpose of evaluating both healthcare attention for patients with anxiety as well as the possible impact of the implementation of the guideline. It was not the intention of the authors to design an exhaustive and detailed evaluation that involves the use of all of the proposed indicators. The objective was to provide a tool for interested clinics and managers, which could be useful in the specific design of the evaluation of the care received by patients with anxiety disorders in Primary Care.

Two types of indicators are proposed:

- **Tracking indicators:** This set of indicators is intended to track the distribution of patients based on the use of the evaluation tools and treatments proposed in the guideline.
- **Compliance indicators:** These are based on the recommendations proposed in this guideline, and therefore on the available scientific evidence and the consensus of healthcare professionals. Although the proposed compliance standards should be 100%, the reality of the context of PC was taken into account when establishing these standards.

Evaluation criteria	Tracking indicators
1. Anxiety diagnosis	Percentage of patients with Generalized Anxiety Disorder, Panic Disorder, and/or Panic Attacks, out of the overall number of patients attended in Primary Care
2. Treatment options	Of the patients with Generalized Anxiety Disorder, Panic Disorder and/or Panic Attack, the number who receive psychological, pharmacological, combined (psychological and pharmacological), or other treatments
3. Use of scales	Percentage of patients with Generalized Anxiety Disorder, Panic attack and/or Panic Attack who are being evaluated with the scales proposed in this guideline
4. Referral to Specialized Mental Health Care	Percentage of patients with Generalized Anxiety Disorder, Panic Disorder, and/or Panic Attacks, referred to Specialized Care out of the overall number of patients with these disorders attended in Primary Care

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Good practice criteria	Compliance indicators	Standard
1. Anxiety diagnosis	1. Percentage of patients diagnosed with Generalized Anxiety Disorder following the clinical criteria established in this guideline 2. Percentage of patients diagnosed with Panic Disorder with/without Agoraphobia following the clinical criteria established in this guideline 3. Percentage of patients diagnosed with Panic Attack following the clinical criteria established in this guideline	90%
2. Information for the patient	1. Percentage of patients with anxiety orders to whom the information on their disorders is offered: treatment options, evolution, and handling of anxiety, reflected in the guideline	100%
3. Treatment options	1. Percentage of patients with Generalized Anxiety Disorder, Panic Disorder and/or Panic Attack, who receive psychological treatment according to the proposed criteria 2. Percentage of patients with Generalized Anxiety Disorder, Panic Disorder and/or Panic Attack, who receive pharmacological treatment according to the proposed criteria 3. Percentage of patients with Generalized Anxiety Disorder, Panic Disorder and/or Panic Attack, who receive other treatments (self-help, medicinal herbs) according to the proposed criteria	80%
4. Referral to Specialized Mental Health Care	1. Percentage of patients with Generalized Anxiety Disorder, Panic Disorder and Panic Attack referred to Specialized Care based on the criteria proposed in this guideline	80%

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10. Recommendations for future research

10.1. Generalized Anxiety Disorder (GAD)

10.1.1. Psychological therapies

Additional studies should be done to determine whether psychodynamic therapies and other techniques such as brief family therapy and counseling are effective for treating patients with GAD, and comparative studies should also be done on these therapies with CBT to determine which is the most useful for treating this disorder.

Within the context of Primary Care in Spain, future studies should advance in the knowledge of the effect of these psychological therapies, measuring the long-term effects, including control groups, blind procedures, all assessing the effect on the consumption of psycho-active drugs.

10.1.2. Pharmacological treatment

Since GAD is generally a chronic disorder, longer RCTS need to be done to draw conclusion regarding the long-term effectiveness of the drugs, and questionnaires need to be used that include indicators to measure the quality of life of the patients with the medication used.

More studies are needed to compare the effectiveness of new anti-depressants, such as duloxetine, with that of other anti-depressants for which there is already sufficient evidence available.

10.1.3. Combined treatment

More studies are needed to directly compare the combined treatment of CBT and pharmacotherapy with both therapies separately, taking into account the long-term results and the organizational mechanism reflected by clinical practice.

These studies should also examine patient preferences for each one of the possible therapies.

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10.2. Panic Disorder with or without agoraphobia (PD)

10.2.1. Psychological therapies

Longer studies need to be done on psychological interventions based on CBT for patients with PD, to evaluate the long-term effects of treatment and the consequences of interruption of the treatment. Also, as result variables, frequency of panic attacks, along with other variables such as anticipatory anxiety should also be included, in addition to criteria for all of the aspects of the illness (cognitive, behavioral, and "arousal" or activation state).

The effectiveness of psychodynamic psychotherapy on patients with PD should be better evaluated, homogenizing the study design and always using randomized controlled studies whenever possible. The effectiveness of other therapies such as brief family therapy and counseling for patients with PD should also be evaluated.

The effect of the psychological interventions currently available in Primary Care should be studied with methodologically appropriate controlled and randomized trials, also evaluating the effect on the consumption psycho-active drugs in patients with PD.

10.2.2. Pharmacological treatment

As already mentioned in the case of GAD, studies need to be done on anti-depressants in patients with PD, studying the long-term effect of these drugs. The effectiveness of the anti-depressants also needs to be compared not only with a placebo, but also among the different drugs.

10.2.3. Combined treatment

The existence of possible long-term negative effects of the combination of CBT and pharmacotherapy should be evaluated. Proper blind RCTS should be done with a number of completely recovered PD patients, without additional treatment during the follow-up, to confirm that the combined treatment does not complicated or interfere with psychotherapy in the long term.

Strategies need to be developed and evaluated to treat patients with refractory PD or patients who respond only partially to therapies.

More studies are needed to research the effects of the combination of anti-depressants with non-cognitive-behavioral therapies, such as psychodynamic therapies.

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10.3. Panic attack

The effectiveness of both pharmacological (BDZ, other drugs) and non-pharmacological interventions in patients with panic attacks needs to be evaluated using variables such as time to recovery from the crisis and prevention of panic attacks.

10.4. Other treatments

10.4.1. Self-help treatment-bibliotherapy

Longer-duration studies are needed, based on larger samples that are able to control the large number of variables that may be skewing the results, to precisely evaluate the clinical effectiveness, maintenance of the benefits achieved long-term, and the optimal selection of material for each type of patient.

In the context of Primary Care, the viability of the directed use of self-help should be examined, evaluating the benefits of its use, determining the optimum length of the intervention in each case, as well as how much professional participation is required to produce a positive change in patients with anxiety disorders.

10.4.2. Herbal medicines

Additional studies are required, if possible, well-designed trials with a sufficient number of patients, to compare the effect of medicinal herbs with other treatments used in anxiety disorders, to make it possible to draw more robust conclusions regarding the effectiveness and safety of this therapy as a treatment option.

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11. Appendices

Appendix 1. Levels of evidence and grades of recommendation (SIGN)[214]

Levels of evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 +	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Studies classified as 1- and 2- should not be used in the process of preparing recommendations due to the high possibility of bias.

√[1]	Recommended best practice based on the clinical experience of the guideline development group

1. In some cases, the guide-preparation team observes that there are important practical aspects that they would like to emphasize and for which there is probably no supporting scientific evidence. In general, these cases are related to some aspect of the treatment that is considered to be good clinical practice and that is not normally questioned. These aspects are classified as points of good clinical practice. These messages are not alternatives to the recommendations based on scientific evidence, but rather should be considered only when there is no other way to highlight the aspect in question.

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Appendix 2. Anxiety measurement instruments

HAD[57]: Hospital, anxiety, and depression (self-administered)

Doctors understand the importance of emotional factors in the majority of illnesses. If the doctor knows the emotional state of the patient, it will be possible to provide better assistance.
This questionnaire was prepared to help your doctor to determine how you are feeling affectively and emotionally. You don't have to pay attention to the numbers on the left. Read each question and underline the response that you feel describes your own emotional state over the last week.
Don't think about each response for too long: in this questionnaire, spontaneous responses are better than the ones that you think about a lot.

A.1. I feel tense or 'wound up' :

3. Most of the time
2. A lot of the time
1. From time to time, occasionally
0. Not at all

D.1. I still enjoy the things I used to enjoy:

0. Definitely as much
1. Not quite so much
2. Only a little
3. Hardly at all

A.2. I get a sort of frightened feeling as if something awful is about to happen:

3. Very definitely and quite badly
2. Yes, but not too badly
1. A little, but it doesn't worry me
0. Not at all

D.2. I can laugh and see the funny side of things:

0. As much as I always could
1. Not quite so much now
2. Definitely not so much now
3. Not at all

A.3. Worrying thoughts go through my mind

3. A great deal of the time
2. A lot of the time
1. From time to time but not too often
0. Only occasionally

D.3. I feel cheerful:

3. Not at all
2. Not often
1. Sometimes
0. Most of the time

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HAD[57]: Hospital, anxiety, and depression (self-administered)

A.4.	**I can sit at ease and feel relaxed:** 0. Definitely 1. Usually 2. Not often 3. Not at all
D.4.	**I feel as if I am slowed down:** 3. Nearly all the time 2. Very often 1. Sometimes 0. Not at all
A.5.	**I get a sort of frightened feeling like 'butterflies' in the stomach:** 0. Not at all 1. Occasionally 2. Quite often 3. Very often
D.5.	**I have lost interest in my appearance:** 3. Definitely 2 I don't take so much care as I should 1. I may not take quite as much care 0. I take just as much care as ever
A.6.	**I feel restless, as if I have to be on the move:** 3. Very much indeed 2. Quite a lot 1. Not very much 0. Not at all
D.6.	**I look forward with enjoyment to things:** 0. As much as ever I did 1. Rather less than I used to 2. Definitely less than I used to 3. Hardly at all
A.7.	**I get sudden feelings of panic:** 3. Very often indeed 2. Quite often 1. Not very often 0. Not at all
D.7.	**I can enjoy a good book or radio or TV programme:** 0. Often 1. Sometimes 2. Not often 3. Very seldom

Score: a score between 0 and 7 does not indicate a case, between 8 and 10 a questionable case, and scores of more than 11 are probably cases in each one of the sub-scales.

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GADS[56]: Goldberg anxiety and depression scale (clinician administered) (Version adapted to Spanish by A. Lobo and cols.)

This is a scale that is very simple to use and highly effective in detecting depression and/or anxiety disorders.
It is also an instrument for evaluating the severity and evolution of these disorders. It can also be used as a guideline for the interview.

Instructions for administering:

- Aimed at the general population.
- This is a clinician-administered questionnaire with two sub-scales:
  - One for detecting anxiety and one for detecting depression.
  - Both scales have 9 questions.
  - The last 5 questions in each scale are only asked if the responses to the first 4 questions, which are required, are positive.
- The probability of suffering a disorder is greater the higher the number of positive responses.
- The symptoms included in the scales refer to the 15 days prior to the visit.
- All of the items have the same point values..
- They follow an order of increasing severity.
- The last items in each scale appear in patients with the most severe disorders.

Anxiety sub-scale:

- Have you felt keyed up, on edge?
- Have you been worrying a lot?
- Have you been irritable?
- Have you had difficulty relaxing?

(If there are 3 or more affirmative responses, continue with questions)

- Have you been sleeping poorly?
- Have you had headaches or neck aches?
- Have you had any of the following: trembling, tingling, dizzy spells, sweating, frequency, diarrhoea?
- Have you been worried about your health?
- Have you had difficulty falling asleep?

Total anxiety:

Depression subscale:

- Have you had low energy?
- Have you had loss of interests?
- Have you lost confidence in yourself?
- Have you felt hopeless?

(If the response to any of the previous questions is affirmative, continue)

- Have you had difficulty concentrating?
- Have you lost weight (due to poor appetite)?
- Have you been waking early?
- Have you felt slowed up?
- Have you tended to feel worse in the mornings?

Total depression:

Evaluation criteria:

Anxiety sub-scale: 4 or more affirmative responses.

Depression subscale: 2 or more affirmative responses.

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Appendix 3. Interview questions to screen for anxiety symptoms and specific anxiety disorders

Questions	Responses
Part 1: Identify anxiety "How have things been going for you recently?" "Any problems with excessive stress, worry, or anxiety?"	[IF YES] Could you tell me about that? When did the extra difficulty seem to start? Were there any major changes or stresses in your life at that time?
Part 2: Explore positive responses above with the following types of questions. **Modify questions to patient's responses**	
"What kinds of things do you worry about? Do you worry excessively about everyday things like your family, your health, work, or finances? Do friends or loved ones tell you that you worry too much? Do you have difficulty controlling your worry, such that the worry keeps you from sleeping or makes you feel physically ill with headaches, stomach troubles, or fatigue?"	[IF YES] Could you tell me about that? **See section on GAD**
"Do you have times when you experience a sudden rush of symptoms or uncomfortable physical feelings such as racing heart or dizziness? Do you have feelings of fear or panic at these times? Have these spells ever occurred out of the blue, without any obvious trigger or cause?"	[IF YES] Could you tell me about that? **See section on GAD**
"Do you avoid any situations because you might experience these spells of symptoms or feelings of fear or anxiety?" (for example, crowds, enclosed places, driving, leaving the house alone, or other situations)	[IF YES] Could you tell me about that? **See section on GAD**
Part 3: If an anxiety problem is identified, explore whether the problem causes interference or a high level of distress Does this problem with [THE SYMPTOMS DESCRIBED BY THE PATIENT] bother you a lot? Does it interfere with your work, activities, or relationships?	

Adapted from the proposal in the Canadian Guideline[61].

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Appendix 4. Information for the patient

Learning to recognize and handle anxiety

Generalized anxiety and panic



This information was prepared by the Clinical Practice Guideline (CPG) Work Group for the Treatment of Patients with Anxiety Disorders in Primary Care. Health Technology Assessment Unit (UETS) of the Agencia Lain Entralgo. Board of Healthcare of the Region of Madrid.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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- What are the factors that influence anxiety?
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What is anxiety?

Anxiety is a normal part of life and is a common response to people's day-to-day situations. A reaction is generated in response to a signal or threat of danger to confront and respond to it. So a certain degree of anxiety is even desirable for the normal handling of day-to-day demands (preparing for an exam, go to a job interview, having to speak in public, etc.).

Anxiety is an emotion that is accompanied by bodily reactions such as muscular tension, sweating, trembling, shortness of breath, headache, chest or back pain, palpitations, "knots in your stomach", diarrhea, and many others.

When anxiety becomes intolerably intense, or when it limits a person's capacity to adapt, anxiety can affect daily life, and can become a problem.

If you are one of the many people who have anxiety problems, don't lose heart – with proper attention, it can be overcome. If you cannot make the anxiety disappear completely from your life, you can learn to control it.

"I feel bad, I don't know what's wrong with me, I feel dizzy, have a headache, butterflies in my stomach, palpitations… I also have so many things to do that I don't know where to start. I freeze up, can't think clearly… I'm paralyzed."

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What are the factors that influence anxiety?

The causes of anxiety disorders are not completely understood, but it appears that they can be caused by a combination of several factors.

Genetic factors are involved (hereditary and family), neurobiological factors (brain areas and organic substances), psychological, social, and cultural factors. In the process of the appearance of anxiety, both individual predisposition factors (personality) as well as environmental factors are important.

How is it diagnosed?

Your family physician will use different tools to be able to establish the diagnosis of your illness.

- **Clinical History:** the doctor will ask you about different aspects of your family history and other illnesses that you may have.
- **Physical examination:** help your doctor to know whether your symptoms are caused by something other than an anxiety disorder.
- **Questionnaires:** your healthcare centre may use a specific questionnaire to help in the diagnosis or to see the changes that are experienced over time.

To rule out any other illness, your doctor may feel that certain tests are needed.

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What types of anxiety disorders are there?

There are different types of anxiety disorders, but generalized anxiety and panic are the two most common ones in Primary Care.

These two disorders are characterized by the following symptoms:

Generalized anxiety disorder

People who suffer from this disorder present excessive anxiety and worry in regard to day-to-day activities or events, which, when it persists over time and is constant, may be very bothersome due to the presence of some or all of the following physical symptoms:

- Restlessness or impatience
- Fatigue
- Difficulty concentrating or drawing a blank
- Irritability
- Muscle tension
- Sleep alterations
- Trembling, sweating, hot flashes

"I don't recognize myself. I'm not myself. I'm exhausted even though I don't don anything. I can't sleep and I'm nervous and very irritable. Everything scares me. I distrust others and think that they think badly of me. I distance myself from my family, from my friends…I'm isolating myself more and more."

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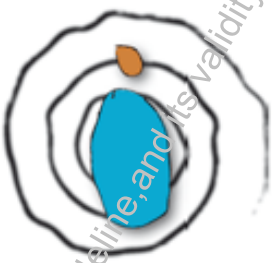
Panic disorder

Panic disorder is characterized by the appearance of panic attacks* that cause:

- Persistent apprehension due to the possibility of having more attacks.
- Concern for the implications of the attack or its consequences (e.g. losing control, suffering a heart attack, "going crazy").
- Changes in behavior related to the crisis, such as what are known as "agoraphobia and avoidance behavior". Specific situations and places are feared and avoided, such as: traveling on a train, subway, or bus, going to shopping centres, places with lots of people, or where you cannot get out easily.

***Panic attack**

This is the main symptom of panic disorder. It is characterized by the sudden appearance of uncontrollable fear or intense discomfort that begins suddenly and reaches its maximum intensity within the first 10 minutes, and may last up to 1 or 2 hours, with physical symptoms such as:



- Tightness, feeling of suffocation
- Palpitations, heart pounding
- Sweating, shivering, or asphyxiation
- Nausea, feeling of choking
- Dizziness or fainting

"I can't take it any more, I'm suffocating…my heart is going to jump out of my chest, I'm losing my mind, I'm going to go crazy. Don't touch me, don't talk to me… I'm going to explode."

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What are the treatment options?

There are several objectives of the treatment of your anxiety problem:

- Relieve the symptoms and prevent relapses.
- If you have panic attacks, to reduce their frequency, duration, and intensity, and reduce avoidance behavior.

The usual treatments are psychotherapy and medication, which may or may not be used together, depending on the type of anxiety disorder that you have.

Psychotherapy

Individual or group psychological interventions, with different degrees of complexity, aimed at treating and modifying the emotional, thought, and behavioral factors that maintain the anxiety and/or its consequences.

Medication

Anti-depressants and anxiolytics are the most commonly-used medications for the treatment of anxiety.

Your family physician is the proper person to tell you which drug is most convenient, how long it is needed, and the possible side effects that it could cause.

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Other treatments

- **Self-help treatments:** Reading and applying specific self-help programs for anxiety problems (text with a programmed sequence of exercises to learn to handle and control anxiety).
- **Medicinal herbs:** Some herbs such as valerian, passion flower, ginkgo biloba, and kava extract* appear to reduce anxiety symptoms, but more research on their safety and effectiveness is needed.

Inform your doctor in regard to any substance, medicine, herbal product, or alternative medicine that you are taking.

Evaluate the possibilities available in your healthcare centre with the professional staff and discuss the treatment to be followed with them. Your opinion is very important when deciding.

In some cases, your doctor may feel that you need to be referred to a specialist.

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* The Spanish medicine and healthcare products regulatory agency included in 2004, the medicinal plant Kava in the list of plants whose sale to public was forbidden or restricted due to hepatic toxicity.

How do anxiety and panic evolve?

Anxiety problems go through periods in which symptoms are reduced or disappear for a variable period of time.

As with other chronic illnesses (diabetes, hypertension, etc.), with proper treatment, it is possible to live with this problem and restore your life to normality. So don't suffer unnecessarily and visit your healthcare centre as soon as possible, because the evolution your problem will improve the sooner it is detected.

Effective treatment will help you to reduce the symptoms, improve your self-esteem, and allow you to enjoy life once again.

There are often ups and downs during the process, but the obstacles and steps backwards are a normal part of the learning process. Don't get discouraged.

"I'm coming out of it…little by little, with effort and help, I'm doing it. It's a hard and painful path, but it's worth it. Now I know that I can beat it."

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What should I keep in mind when I visit my healthcare centre?

It is important that the stigma that surrounds this type of disorder not prevent you from seeking professional help. Visit your healthcare centre. The following are some useful tips for your next visit to your family physician.

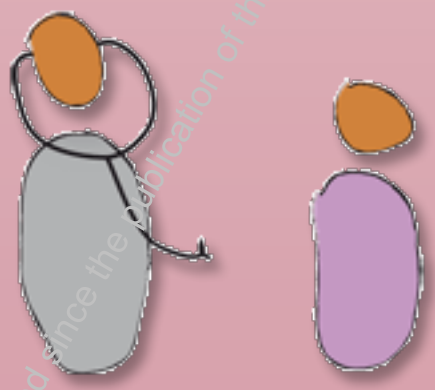
- You can trust the professionals at your healthcare centre. They are people close to you, and they will understand your doubts, fears, and problems.
- Prepare what you want to say to the doctor beforehand. - Tell your doctor your physical and emotional symptoms. It may be helpful if a family member or friend accompanies you.

- Don't be afraid to ask any questions that are still unclear to you.

- It is essential that you express your preferences in regard to the different treatment options.

Keep in mind that ***you are the most important part of this process.***

"And who can I tell about what's happening to me? I'm embarrassed and afraid. I don't even understand myself. How can someone else understand me?... I feel so alone. I need help but don't know where to turn."



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How can I deal with my anxiety so that it will improve?

Advice for handling your anxiety

- If you are doing psychotherapy, at home, it is important to practice the exercises learned in therapy, such as relaxation and breathing, because they will be of great use to you.
- Medication sometimes has disagreeable side effects, which normally disappear or diminish after the first few weeks, but you have to remember that the most important thing is to continue with the treatment and not interrupt it.
- Plan your daily tasks rationally, prioritize your needs, and if for some reason you can't do everything, remember that another day will come after today.
- Try to leave space everyday to include activities that will be enjoyable and fun among your tasks: read, listen to music, exercise, take a walk, anything that is relaxing for you.
- Don't stop doing the activities that give you the feeling of "recharging your batteries". Energy needs to be restored.
- Don't "accelerate". Remember that doing things faster doesn't make you more efficient.
- Learn to handle your feelings. Positive thoughts also have a positive effect on your mood.
- It's important to recognize oppressive thoughts, in those situations that worry you (the "all", "nothing", "always", "never", "nobody") and replace them with other more rational ones ("something", "some", "sometimes").
- Take advantage of your mistakes and learn from them. To err is human and you don't have to do your tasks to perfection.
- Eat a balanced diet and try to eliminate or reduce the intake of substances that are bad for anxiety, such as: caffeine and other beverage stimulants.
- Remember that alcohol, cocaine, cannabis, and synthetic drugs can produce anxiety.
- If your sleep habits are not satisfactory, try to modify them. Try to get as much sleep as you need to rest.

Lastly, remember that you can learn to control anxiety and reduce it progressively.

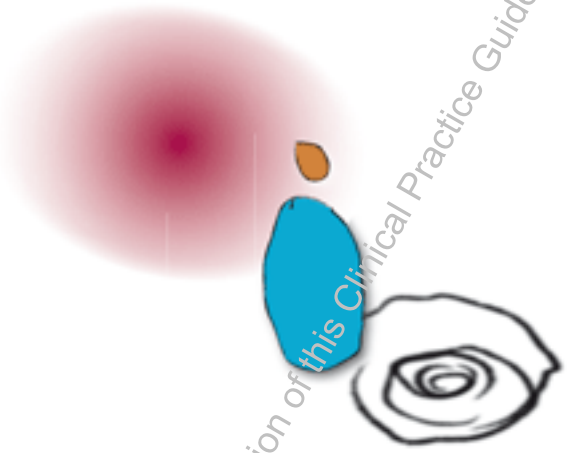
"I've learned how to relax, avoid stimulants, I exercise, and that helps me sleep. I plan the activities that are more difficult for me to do…I've regained hobbies that I had completely forgotten."

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Recommendations for overcoming your panic attack

- It's important to remember that you are not facing a danger that is as serious as you may believe. Nothing worse will happen.
- Don't allow panic to increase with other scary thoughts. Interrupt what you are thinking and you'll notice that the fear will begin to disappear on its own.
- Try to calm down and relax little by little.
- Relax and slow your breathing. Imagine that you are a balloon that slowly inflates and then deflates.
- Wait and give the fear time to pass.
- Think of the progress that you've made thus far, despite all of the difficulties. Think of how satisfied you will feel when you succeed.
- When you start to feel better and are ready to continue, start out relaxed and calm. There is no need for effort or rushing.
- Try to distract yourself, now that the nervousness has diminished. Talk with someone, take a walk, etc.

The more you learn how to handle fear, the less afraid you'll be and you'll feel freer!!



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How can my family and friends help me?

Your family and friends play a very important role in this whole process. For this reason, there are some recommendations specifically for them. It is important:

- Not to trivialize what is happening and make the person feel understood.
- To listen without being critical; avoid the "come on, it's nothing."
- To accompany the person to the healthcare centre if necessary or helpful.
- To inform yourself regarding the type of treatment that the person is following. Knowing the different treatment options also helps to learn more about anxiety.
- To observe and pay attention to changes in the behavior of the person who has the problem.
- To encourage the person to do activities that may be enjoyable or fun.
- To support the person to face his or her fears, always by mutual agreement and without pressuring.
- To help the person obtain additional useful information about anxiety.

"I'm still in treatment…and thanks to that and the help of my family, I'm doing better."

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Where can I learn more about anxiety?

Associations of patients and families

- **FEAFES: Spanish Confederation of Family Groups and Individuals with Mental Illness**
  Telephone: 91 507 92 48 (Madrid)
  E-mail: feafes@feafes.com
  Website: www.feafes.com/
- **FEMASAM: Madrid Federation of Mental Health Associations**
  Telephone: 91 472 98 14 (Madrid)
  E-mail: info@femasam.org
  Website: www.femasam.org/
- **ACTAD: Catalan Association for the Treatment of Depression and Anxiety Disorders (formerly AADA and Camins Oberts)**
  Telephone: 93 430 12 90 (Barcelona)
  E-mail: info@actad.org
  Website: www.actad.org/
- **Associació Gironina d'Agorafóbics**
  Telephone: 669 00 78 87 (Girona)
  E-mail: quimvencells@yahoo.es
  Website: http://www.agorafobia.es.vg/
- **Association of Anxiety Disorders – Mutual Assistance Groups**
  Telephone: 646 71 53 94 and 666 29 29 73 (Barcelona)
  E-mail: atagam@ansietat.org
  Website: http://www.ansietat.org/
- **ADEA: Albacete Association of Agoraphobia Sufferers**
  Telephone: 967 61 18 83 and 967 52 31 44 (Albacete)
  E-mail: adealba_2000@terra.com
  Website: http://www.geocities.com/adealba_2000/index.html
- **AMADAG: Madrid Panic and Agoraphobia Association**
  Telephone: 617 83 79 30 (Madrid)
  E-mail: amadag_asociacion@hotmail.com
  Website: http://www.amadag.com/
- **A.C.E.D.: Association against stress and depression**
  Telephone: 91 532 84 14 (Madrid)
  E-mail: aced@estresydepresion.org
  Website: http://www.estresydepresion.org/index.html

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- **AGORAMUR: Association for anxiety, panic and/or agoraphobia sufferers of Murcia**
  Telephone: 654 52 94 48 (Madrid)
  E-mail: agoramur@hotmail.com
- **ASATRA: Aragon Association of Anxiety Disorders (Zaragoza)**
  Telephone: 687 47 76 69 (Madrid)
  E-mail: asociacion-asatra@hotmail.com
- **CAPAZ: Aragon Panic and Agoraphobia Centre – Zaragoza collective of panic and agoraphobia sufferers**
  Telephone: 976 25 98 07 (Zaragoza)
- **AGOS: Association of persons affected by anxiety disorders and agoraphobia of the province of Cadiz**
  Telephone: 956 27 19 37 (Cádiz)
  E-mail: carmenblanca35@hotmail.com
- **Leku irekiak - A.A.D.A.: Association for Agoraphobia Assistance and Awareness of the Basque Country**
  Telephone: 94 493 78 33
  E-mail: lekuirekiak@terra.es
  Website: www.terra.es/personal6/lekuirekiak/
- **Horizontes Abiertos**
  Telephone: 928 24 91 68 (Las Palmas de Gran Canaria)

Internet Resources

- www.centrodeapoyoapa.org (American Psychology Association)
- www.lasalud.com/pacientes/ansiedad.htm
- www.nlm.nih.gov/medlineplus/spanish
- www.juntospodemos.com/

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Useful references

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Appendix 5. Glossary and abbreviations

Glossary

AGREE (Appraisal of Guidelines, Research and Evaluation for Europe): International initiative to facilitate the design and evaluation of clinical practice guidelines.

DALY (Disability-adjusted life year): Measurement of the overall burden of illness that reflects the number of years that a person could have lived, lost due to premature decease, and the year of productive life lost due to disability.

Bibliotherapy: Guided use of reading for therapeutic purposes. This consists of the acquisition of therapeutic knowledge and practices through reading a specifically selected bibliography recommended by the therapist.

Cochrane Library: An effectiveness database produced by the Cochrane Collaboration, made up of, among other things, the original systematic reviews by the organization.

DSM-IV: Fourth edition of the *Diagnostic and Statistical manual of the mental disorders* **by the American Psychiatric Association.** This is a classification of mental disorders into different types based on a series of criteria with defining traits. It is prepared for clinical, educational, and research use. Its purpose is to provide clear descriptions of the diagnostic categories, so that clinics and researchers can diagnose, study, and exchange information, and treat the different mental disorders.

RCT (Randomized Clinical Trial): This is a study designed so that subjects are randomly assigned to two groups: one (experimental group) receives the treatment that is being tested, and the other (comparison or control group) receives a standard treatment (or sometimes a placebo). The two groups are monitored to observe any differences in the results. The effectiveness of the treatment is evaluated this way.

Multi-axial axes in the DSM-IV: Evaluations on multiple axes, each of which concerns a different area of information that can help the clinician to plan treatment and predict results.

Embase: European (Dutch) database produced by Exerpta Médica with pharmacology and clinical medicine content.

Open trial: 1. Clinical trial in which the researcher knows the intervention that is given to each participant. **2.** Clinical trial with open sequential design.

In-depth interview: A qualitative research technique to obtain information using a conversation between an informant with a series of previously established characteristics and an interviewer.

Blind or double-blind trial: Clinical trials in which neither the participants (blind) nor the medical personnel (double blind) know which of the possible therapies each individual is receiving.

Case-control study: A study that identifies persons with an illness (cases), lung cancer for example, and compares them with a group without the illness (control). The relationship between one or more factors (tobacco, for example) related to the illness is examined, comparing the frequency of exposure to that or other factors between the cases and the controls.

Cohort study: This consists of following one or more cohorts of individuals who present different degrees of exposure to a risk factor in whom the appearance of the illness or condition being studied is measured.

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Cross-sectional-Descriptive Study: This is a study that describes the frequency of an event or an exposure at a given time (single measurement). It makes it possible to examine the relationship between a risk factor (or exposure) and an effect (or result) in a defined population and at a given time (a cut). Also called prevalence studies.

Exposure: This is a type of behavioral therapy that involves the deliberate exposure to situations that were previously avoided or feared stimuli. This can be done by asking the person to imagine these situations, especially when direct exposure is impractical or difficult, a mode that is called *in vitro*, interceptive, or imaginary. On the other hand, exposure may also be *in vivo*, or exteroceptive through real stimuli or situations.

Discussion group: Qualitative research technique that is used to identify attitudes, positions, evaluations, or perceptions regarding something or someone that are held by a group of individuals.

Confidence interval: This is the interval within which the true magnitude of the effect (which is never exactly known) is found with a pre-established degree of security or confidence. They often talk about "95% confidence interval" (or 95% confidence limits). This means that within that interval, the true value would be found in 95% of the cases.

Qualitative research: This is a methodology that covers a variety of theoretical trends, methods and techniques, and is characterized by the study of phenomena in their natural context, attempting to make sense of or interpret them based on the meanings that people give them. This is done using empirical materials (interviews, observations, texts, etc.) that can best describe both routine and problematic situations and what they mean in the lives of the individuals.

Medline: Predominantly clinical database produced by the US National Library of Medicine, available on CD-Rom and on the internet (PubMed).

Meta-analysis: This is a statistical technique that makes it possible to integrate the results of different studies (studies of diagnostic tests, clinical trials, cohort studies, etc.) into a single estimator, giving more weight to the larger studies.

Morbidity: Illness or frequency in which an illness is present in a population.

Mortality: Death rate or number of deaths due to a particular illness in a group of people and a specified period of time.

NICE: Forms part of the NHS ("National Health Service" of England). Its role is to provide doctors, patients, and the general public with the best evidence available, mainly in the form of clinical guidelines.

Participant observation: This is a qualitative research technique that establishes a deliberate communication between the observer and the observed phenomenon. The researcher gathers the keys of what is observed, interprets what is occurring, and thus obtains a systematic and complete knowledge of the observed reality.

Placebo: A substance administered to the control group of a clinical trial, ideally identical in appearance and taste to the experimental treatment, which is believed to have no specific effect for the illness being studied. In the context of non-pharmacological interventions, the placebo is usually referred to as simulated treatment.

Prevalence: The proportion of people with a finding or illness in a particular population, at a given time.

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Breathing retraining: This is an intervention that encourages people who hyperventilate to reduce their respiratory frequency using the diaphragm.

Cognitive restructuring: This is an intervention that involves asking questions to help people to question stereotypical and repetitive thoughts and images that increase fear, replacing these irrational or distorted thoughts with other more rational ones.

Applied relaxation: Training in relaxation techniques and self-control of the symptoms, without questioning beliefs. It is based on the principle that when the person learns deep muscle relaxation, it reduces body tension and the anxiety that is felt.

Systematic review (SR): This is a review in which the evidence on a question has been systematically identified, evaluated, and summarized according to a series of predetermined criteria. It may or may not include meta-analysis.

Case series: Analysis of series of patients with the illness.

SIGN: A multi-disciplinary agency in Scotland that prepares clinical practice guidelines based on the evidence, as well as methodological documents on how the guidelines should be designed.

Abandonment rate: The number of people who abandoned during the trial and the later specific exclusions from the random assignment.

Cognitive-Behavioral Therapy (CBT): This is a form of structured psycho-therapeutic intervention that uses different techniques to try to change dysfunctional beliefs and negative automatic thoughts.

Tolerance: The state present when the body becomes accustomed to a medication, so that a larger amount of the medication is needed.

Abbreviations

AD: Anti-depressants

TAD: Tricyclic Anti-depressants

SC: Specialized Care

AEN: Spanish Neuropsychiatry Association

AGREE: Appraisal of Guidelines Research and Evaluation

AMADAG: Madrid Panic and Agoraphobia Association

PC: Primary Care

DALY: Disability-Adjusted Life Years

BDZ: Benzodiazepines

CAS: Clinical Anxiety Scale

CGI: Clinical Global Impressions Scale

CINAHL: Cumulative Index to Nursing & Allied Health Literature

CINDOC: Scientific Documentation and Information Centre of the Senior Scientific Research Board

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DARE: Database Abstracts of Reviews Effects

EMDR: Eye Movement Desensitization and Reprocessing

GADS: Goldberg Anxiety and Depression Scale

RCT: Randomized Clinical Trial

ALS: Amyotrophic Lateral Sclerosis

EMDR: Eye Movement Desensitization and Reprocessing

FDA: Food and Drug Administration

FEAFES: Spanish Confederation of Family Groups and Individuals with Mental Illness

FEMASAM: Madrid Federation of Mental Health Associations

FPS: Focused Psychological Strategies

CPG: Clinical Practice Guideline

HAD: Anxiety and Depression Scale

HARS: Hamilton Anxiety Rating Scale

HTA: Health Technology Assessment

CI: Confidence Interval

INAHTA: International Network of Agencies for Health Technology Assessment.

SSRI Seratonin Reuptake Inhibitors

SNSRI: Seratonin and Noradrenalin Reuptake Inhibitors

MHRA: Medicines and Healthcare products Regulatory Agency

MOH: Ministry of Health (Singapore)

NHS: National Health Service

NICE: National Institute for Clinical Excellence

NNT: Necessary number of patients to treat to reduce an event.

PDSS: Panic Disorder Severity Scale

PICO: Patient/Intervention/Comparison/Outcome PQ: Physician Questionnaire

SEMERGEN: Spanish Society of Primary Care Physicians SEMFYC: Spanish Society of Family and Community Medicine SEP: Spanish Psychiatric Society SIGN: Scottish Intercollegiate Guidelines Network

MH: Mental Health

SoMaMFYC: Madrid Society of Family and Community Medicine

STAI: State Anxiety Inventory Scale

PD: Panic disorder

GAD: Generalized anxiety disorder

CBT: Cognitive-Behavioral Therapy

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BFT: Brief Family Therapy

IPT: Interpersonal Therapy

UESCE: Spanish Union of Scientific Nursing Societies UETS: Health Technology Assessment Unit

WONCA: World Organisation of National Colleges, Academies and Academia Associa-tions of General Practitioners/Family Physicians

WP2: Anxious Inhibition Widlocher-Pull Scale

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Appendix 6. Declaration of interest

A conflict of interest occurs under circumstances in which the professional opinion of a primary interest, such as patient safety or the validity of research, may be excessively influenced by other secondary interests, whether this be financial benefit, prestige, or personal or professional promotion.

Several types of financial interactions may be considered in relations between professionals and the healthcare industry (pharmaceutical, healthcare technology, etc.).

- Support and financing of research.
- Employment as a consultant for a pharmaceutical company.
- Shareholder or economic interests in a pharmaceutical company.

In turn, these potential conflicts of interest are considered to be of two types in the preparation of CPGs.

- Personal interests: these involve professional fees or personal benefits for a member of the team.
- Non-personal interests: these involve financing that benefits the department or unit under the management responsibility of a member of the team, who does not receive it personally. The economic funding to create a unit or department, financial support for hiring personnel for those units, and financing of research in the unit can be considered to fall into this category.

The potential conflict of interest exists regardless of whether or not the professional considers the relations to have an influence on his or her scientific criteria. The following is a form on the declaration of conflicts of interest designed for the purpose of covering the aforementioned aspects.

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Conflict of Interest Statement

First and Last name: _____

_____

Profession: _____

Institution for which you work:

Name of the centre: _____

Address: _____

City: _____

Postal Code: _____

Institution that you represent (association, scientific society, etc. – answer only if different from the one specified above):

_____

Contact telephone (reachable): _____

Email for sending documentation (@): _____

Mr./Ms. _____

with National Identity Document _____, after reading the policy of the Preparation program for Clinical Practice Guidelines (CPG) based on evidence, to assist in clinical decision-making in the National Healthcare System (SNS) in regard to conflicts of interest, I hereby declare that I DO ☐ DO NOT ☐ have conflicts of interest in regard to the activities related to the subject that is the object of the CPG within **the last three years.**

If so, specify what the conflicts are in tables 1 to 3.

Signature Date: February 22, 2007

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Table 1. Personal interests

	Activity	Institution	Date
Financing for participating in a study			
Consulting for a pharmaceutical or other technological company			
Shareholder/commercial interests in a company (patents…)			
Economic interests in a private company related to healthcare (as the owner, employee, shareholder, private consultant…) that could be significant in relation to the preparation of the guideline			
Non-economic conflicts of interest that could be significant in the preparation of the guideline			

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Table 2. Non-personal interests

	Activity	Institution	Date
Financing or economic funding for the creation of a unit or service			
Significant allocation of material to the unit or services			
Hiring or economic funding to hire personnel in the unit or services			
Economic funding to finance a research study			

Table 3. Other possible conflicts of interest not indicated in the previous sections (specify)

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