Clinical Practice Guideline for the Treatment of Generalised Anxiety Disorder in Primary Care

Short version

Clinical Practice Guidelines in the Spanish NHS

Ministry of Health

MINISTERIO DE SANIDAD

Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del Sistema Nacional de Salud

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Clinical Practice Guideline for the Treatment of Generalised Anxiety Disorder in Primary Care

1. Introduction

The overall aim of the Clinical Practice Guideline for the Treatment of Generalised Anxiety Disorder in Primary Care is to provide up-to-date, systematic, evidence-based recommendations to help healthcare professionals and adults with GAD make decisions about the most appropriate therapeutic options when managing their health problem in primary care (PC), with the aim of improving the quality of care provided to these patients, in the hope of improving their quality of life.

This English version contains the following information:

- **Clinical questions**
- **Recommendations**
- **Rationale**
- **Complete clinical question** (link to the Spanish version)
- **References**

The full version (in layered format and PDF), the methodological material, the patient material and other information are available in Spanish at the following link:

https://portal.guiasalud.es/gpc/tratamiento-trastorno-ansiedad-generalizada-atencion-primaria

2. Initial care strategy

• Question

What should be the first steps in primary care for the assessment and initial management of adults with GAD?

• Recommendations

GOOD CLINICAL PRACTICE

1. In the therapeutic approach to GAD in PC, it is suggested that a stepwise strategy be followed in the order as the recommendations below.

2. A comprehensive initial evaluation of the patient with GAD is suggested to determine its severity through a clinical interview and with the help of validated measurement tools or scales, including:

    - Nature, severity and duration of the symptoms.
    - Behavioural, cognitive and physiological symptoms and responses to anxiety (e.g., excessive sweating, heart palpitations, trembling, persistent worry, avoidance behaviours, reassurance seeking, safety seeking).
    - Anxiety triggers
    - Degree of distress and functional impairment.
    - Coexistence of other psychopathologies such as mood disorders, other anxiety disorders, substance use disorders, personality disorders or other comorbidities, and the possible interactions between treatments.
    - Presence of suicidal thoughts or behaviour.
    - Experience with previous or current treatment for this or other psychopathologies, including therapeutic response and adverse effects.
    - Personal and family history of mental disorders.
    - Social context and personal circumstances (e.g., presence of family support, quality of interpersonal relationships, presence in social networks, living conditions, employment, immigration status).
    - Factors that could maintain the disorder or limit recovery.

3. It is suggested that information on the nature, treatment and self-monitoring of GAD, tailored to the characteristics of the patient, be offered to all patients and their families, regardless of the severity of the process.

4. As a first step in the treatment of GAD in PC, it is suggested that psychoeducation including strategies for self-managing anxiety and advice on healthy lifestyle habits (such as regular exercise, healthy diet, sleep hygiene and reduction of tobacco, alcohol and other harmful substances and addictions) be provided. It is also suggested that patients receive written information and that peer support, social prescribing activities participation in health education programmes, and group workshops led by the healthcare professional (i.e., nurse) be encouraged where available.

5. It is suggested that patients diagnosed with GAD be offered self-help resources, whether or not they are guided by a healthcare professional (i.e., medical, psychological, or nursing professional) which meets the following criteria:

- Include written or electronic materials adapted to the age and characteristics of the patient, based on cognitive behavioural therapy.
- Suggest that the patient puts into practice the recommendations included in the material for at least 4-6 weeks.
- Ensure at least minimal contact (by telephone or in person) with the healthcare professional (i.e., medical, psychological or nursing professional) to guide the process.

6. It is suggested that self-management and the patient's active involvement in monitoring their improvement and in developing and adhering to their treatment plan should be encouraged in conjunction with the treating healthcare professional(s) (i.e., through shared decision-making between the patient and the healthcare professional(s) - medical, psychological, nursing professional). The use of a questionnaire-based assessment tool is suggested to evaluate improvement and adherence to treatment.

7. In patients with GAD, it is suggested to routinely assess the presence of different comorbidities such as other anxiety disorders or depression.

8. When choosing a treatment for GAD, it is suggested that the severity of the disorder, evidence of efficacy and safety, previous experience, patient's preferences, accessibility, cost and tolerability should be considered.

9. To explore the preferences of the patient with GAD, a shared decision-making process is suggested in which the patient discusses treatment options, the duration and content of treatment, expected outcome and the costs with the treating healthcare professional.

10. Wherever possible and with the patient's consent, it is suggested that the family or others important to the person with GAD be involved in management planning decisions and in supporting the person during treatment.

11. It is suggested that long-term pharmacological treatments should be actively re-assessed for appropriateness.

- ## Rationale

The Guideline Updating Group (GUG) has decided to formulate a series of general practical considerations because it is aware that no scientific evidence has been found to directly answer the research question. These recommendations have been formulated in an attempt to promote appropriate clinical management of patients with GAD attending PC consultations.

In addition to its own clinical experience the GUG has taken into account the recommendations of current CPGs of high methodological quality on GAD.

The GUG believes it is important to take a holistic approach to the patient with GAD, addressing not only the physical sphere, but also the social and psychological ones. To this end, it is recommended that healthcare professionals are familiar with and use all the available tools for accurate detection, identification, diagnosis, and adequate follow-up.

A stepwise therapeutic strategy is recommended, starting with psychoeducation, healthy lifestyle recommendations and self-help programmes, followed by specific treatment,

which should not be limited to pharmacological prescription, but should include the psychological treatments available.

Likewise, prior to starting a new treatment and in order to minimise polypharmacy, drug interaction and side effects, the PC professional should take into account the patient's comorbidities and the treatments that the patient is taking at present.

In addition, the GUG recommends a patient participatory approach, in this sense, the patient, should receive detailed information on the nature and treatment of their illness regardless of its severity, and should take an active interest in monitoring their improvement using assessment tools such as questionnaires, for example, GAD-7 or PSWQ-16, and participate with the treating health professional in the development of their treatment plan.

• Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-1

• References

1. Cordero-Andrés P, González-Blanch C, Umaran-Alfageme O, Muñoz-Navarro R, Ruíz-Rodríguez P, Medrano LA, et al. Tratamiento psicológico de los trastornos emocionales en atención primaria: fundamentos teóricos y empíricos del estudio PsicAP. Ansiedad Estrés. julio de 2017;23(2-3):91-8. DOI: 10.1016/j.anyes.2017.10.004

2. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113] [Internet]. NICE; 2011. Disponible en: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997

3. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12):1109-72. DOI: 10.1177/0004867418799453 DOI: 0004-8674

3. Psychological treatment

3.1 Cognitive behavioural therapy

- **Question**

What is the comparative effectiveness and safety of cognitive behavioural therapy (CBT) in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. In patients with mild or moderate GAD whose symptoms have not improved after an educational intervention including self-management of anxiety and advice on healthy lifestyle, cognitive behavioural therapy is suggested as a first line of psychological treatment. [Strongly in favour]

2. It is suggested that the modality of cognitive behavioural therapy (individual, group, telephone or computer-based) be agreed with the patient, in a shared decision-making process, according to their values and preferences and the available resources, with the aim of increasing acceptability and adherence to it and reducing inequalities in access. [Weak recommendation in favour]

GOOD CLINICAL PRACTICE

3. Wherever possible, it is suggested that cognitive behavioural therapy sessions initially take place on a weekly basis.

4. Initially, it is suggested that the patient be seen weekly to monitor adherence, possible adverse effects and to identify any worsening of symptoms until there is a response and symptoms have stabilised.

5. It is suggested that a review of the response to the initial treatment be conducted after 4-6 weeks of cognitive behavioural therapy (if the sessions are weekly).

6. If there is at least a partial response to the initial treatment within 4-6 weeks of starting treatment, it is suggested that treatment be continued until 8-12 sessions have been completed and that progress be evaluated.

7. It is suggested that the conclusion of the treatment should be planned in a methodological and incremental manner, with sessions gradually spaced out over time. As for instance, in the case of weekly sessions, these could be scheduled every two weeks, then monthly and finally as follow-up and /or prevention relapses sessions.

8. If there is no response to the initial treatment or if the symptoms worsen within 4-6 weeks of starting treatment, it is suggested that a modification of the treatment be considered, consisting of associating pharmacological treatment until symptoms are under control, or offering an alternative psychological therapy.

- **Rationale**

A strong recommendation has been made in favour of the use of CBT in patients with mild or moderate GAD whose symptoms have not improved after the educational intervention and a weak recommendation in favour of the modality of CBT chosen (group/individual/ telephone /computer-based) in accordance with the patient´s values and preferences and the available resources.

The GUG has considered the magnitude of the expected beneficial effects, the benefit-risk balance, the cost-effectiveness and the acceptability of CBT by patients.

In addition, a series of good practice recommendations have been formulated in relation to the implementation of these recommendations. These are relevant clinical considerations regarding the frequency of sessions, monitoring of adherence and response, continuation and completion of treatment and, finally, the alternative to non-response, based on the GUG's clinical practice experience and the recommendations of current high methodological quality CPGs on GAD.

Magnitude of the expected effects: the evidence indicates that the different modalities of CBT (individual/group/telephone/computerised) have significant effects in the reduction of symptoms, the management of concerns and the improvement of psychological functioning.

Benefit-risk balance: the GUG considers that the benefit-risk balance is globally favourable for all modalities of CBT since the demonstrated benefits outweigh the possible associated risks. However, the decision will have to be assessed individually and on a personalised basis to determine the most appropriate modality or option for each patient and their specific situation.

Cost-effectiveness: the evidence indicates that CBT, regardless of its modality, is cost-effective when compared to usual care.

Patients´ acceptability: from the GUG's point of view, the majority of patients, once informed of the pros and cons, would agree to the treatment.

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-2

- **References:**

1. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113] [Internet]. NICE; 2011. Disponible en: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997

2. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12):1109-72. DOI: 10.1177/0004867418799453 DOI: 0004-8674

3. Hoyer J, Becker ES, Margraf J. Generalized anxiety disorder and clinical worry episodes in young women. Psychol Med. 2002;32:1227-37. DOI: 10.1017/s0033291702006360

4. Wetherell JL, Ayers CR, Sorrell JT, Thorp SR, Nuevo R, Belding W, et al. Modular psychotherapy for anxiety in older primary care patients. Am J Geriatr Psychiatry. 2009;17(6). DOI: 10.1097/JGP.0b013e3181a31fb5

5. Power KG, Simpson RJ, Swanson V, Wallace LA, Feistner ATC, Sharp D. A controlled comparison of cognitive- behaviour therapy, Diazepam, and placebo, alone and in combination, for the treatment of generalised anxiety disorder. J Anxiety Disord. 1990;4(4). DOI: 10.1016/0887-6185(90)90026-6

6. Power KG, Jerrom DWA, Simpson RJ, Mitchell MJ, Swanson V. A Controlled Comparison of Cognitive—Behaviour Therapy, Diazepam and Placebo in the Management of Generalized Anxiety. Behav Psychother. 1989;17(1). DOI: 10.1017/S0141347300015597

7. Linden M, Zubraegel D, Baer T, Franke U, Schlattmann P. Efficacy of Cognitive Behaviour Therapy in Generalized Anxiety Disorders. Psychother Psychosom. 2005;74(1). DOI: 10.1159/000082025

8. Bakhshani NM, Lashkaripour K, Sadjadi SA. Effectiveness of short term cognitive behavior therapy in patients with generalized anxiety disorder. J Med Sci. 2007;7(7). DOI: 10.3923/jms.2007.1076.1081

9. Barlow DH, Rapee RM, Brown TA. Behavioral treatment of generalized anxiety disorder. Behav Ther. 1992;23(4). DOI: 10.1016/S0005-7894(05)80221-7

10. Borkovec TD, Costello E. Efficacy of Applied Relaxation and Cognitive-Behavioral Therapy in the Treatment of Generalized Anxiety Disorder. J Consult Clin Psychol. 1993;61(4). DOI: 10.1037/0022-006X.61.4.611

11. Butler G, Fennell M, Robson P, Gelder M. Comparison of Behavior Therapy and Cognitive Behavior Therapy in the Treatment of Generalized Anxiety Disorder. J Consult Clin Psychol. 1991; DOI: 10.1037//0022-006x.59.1.167

12. Zinbarg RE, Eun Lee J, Lira Yoon K. Dyadic predictors of outcome in a cognitive-behavioral program for patients with generalized anxiety disorder in committed relationships: A «spoonful of sugar» and a dose of non-hostile criticism may help. Behav Res Ther. 2007;45(4). DOI: 10.1016/j.brat.2006.06.005

13. Ladouceur R, Dugas MJ, Freeston MH, Léger E, Gagnon F, Thibodeau N. Efficacy of a cognitive-behavioral treatment for generalized anxiety disorder: Evaluation in a controlled clinical trial. J Consult Clin Psychol. 2000;68(6). DOI: 10.1037/0022-006X.68.6.957

14. Nordahl HM, Borkovec TD, Hagen R, Kennair LEO, Hjemdal O, Solem S, et al. Metacognitive therapy versus cognitive–behavioural therapy in adults with generalised anxiety disorder. BJPsych Open. 2018;4(5). DOI: 10.1192/bjo.2018.54

15. van der Heiden C, Muris P, van der Molen HT. Randomized controlled trial on the effectiveness of metacognitive therapy and intolerance-of-uncertainty therapy for generalized anxiety disorder. Behav Res Ther. 2012;50(2). DOI: 10.1016/j.brat.2011.12.005

16. Rezvan S, Baghban I, Bahrami F, Abedi M. A comparison of cognitive-behavior therapy with interpersonal and cognitive behavior therapy in the treatment of generalized anxiety disorder. Couns Psychol Q. 2008;21(4). DOI: 10.1080/09515070802602096

17. Dugas MJ, Brillon P, Savard P, Turcotte J, Gaudet A, Ladouceur R, et al. A Randomized Clinical Trial of Cognitive-Behavioral Therapy and Applied Relaxation for Adults With Generalized Anxiety Disorder. Behav Ther. 2010;41(1). DOI: 10.1016/j.beth.2008.12.004

18. Gosselin P, Ladouceur R, Morin CM, Dugas MJ, Baillargeon L. Benzodiazepine discontinuation among adults with GAD: A randomized trial of cognitive-behavioral therapy. J Consult Clin Psychol. 2006;74(5). DOI: 10.1037/0022-006X.74.5.908

19. Stanley MA, Wilson NL, Novy DM, Rhoades HM, Wagener PD, Greisinger AJ, et al. Cognitive behavior therapy for generalized anxiety disorder among older adults in primary

care: a randomized clinical trial. JAMA. 8 de abril de 2009;301(14):1460-7. DOI: 10.1001/jama.2009.458

20. Stanley MA, Beck JG, Novy DM, Averill PM, Swann AC, Diefenbach GJ, et al. Cognitive-behavioral treatment of late-life generalized anxiety disorder. J Consult Clin Psychol. 2003;71(2). DOI: 10.1037/0022-006X.71.2.309

21. Stanley MA, Hopko DR, Diefenbach GJ, Bourland SL, Rodriguez H, Wagener P. Cognitive-behavior therapy for late-life generalized anxiety disorder in primary care: Preliminary findings. Am J Geriatr Psychiatry. 2003;11(1). DOI: 10.1097/00019442-200301000-00012

22. Stanley MA, Wilson NL, Amspoker AB, Kraus-Schuman C, Wagener PD, Calleo JS, et al. Lay providers can deliver effective cognitive behavior therapy for older adults with generalized anxiety disorder: A randomized trial. Depress Anxiety. 2014;31(5). DOI: 10.1002/da.22239

23. González-Blanch C, Barrio-Martínez S, Priede A, Martínez-Gómez S, Pérez-García-Abad S, Miras-Aguilar M, et al. Cost-effectiveness of transdiagnostic group cognitive behavioural therapy versus group relaxation therapy for emotional disorders in primary care (PsicAP-Costs2): Protocol for a multicentre randomised controlled trial. Moreno-Peral P, editor. PLOS ONE. 16 de marzo de 2023;18(3):e0283104. DOI: 10.1371/journal.pone.0283104

24. Cano-Vindel A, Muñoz-Navarro R, Moriana JA, Ruiz-Rodríguez P, Medrano LA, González-Blanch C. Transdiagnostic group cognitive behavioural therapy for emotional disorders in primary care: the results of the PsicAP randomized controlled trial. Psychol Med. noviembre de 2022;52(15):3336-48. DOI: 10.1017/S0033291720005498

25. Boletín Oficial del País Vasco. Osakidetza Servicio Vasco de Salud [Internet]. 2018 [citado 27 de octubre de 2022]. Disponible en: https://www.euskadi.eus/bopv2/datos/2018/02/1800712a.pdf

26. Health Quality Ontario. Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017;17(15):1-167.

27. National Collaborating Centre for Mental Health (UK). Generalised Anxiety Disorder in Adults: Management in Primary, Secondary and Community Care [Internet]. Leicester (UK): British Psychological Society; 2011 [citado 29 de junio de 2023]. (National Institute for Health and Clinical Excellence: Guidance). Disponible en: http://www.ncbi.nlm.nih.gov/books/NBK83459/ DOI: 978-1-904671-42-8

28. Kumar S, Bell MJ, Juusola JL. Mobile and traditional cognitive behavioral therapy programs for generalized anxiety disorder: A cost-effectiveness analysis. PLoS ONE. 2018;13(1). DOI: 10.1371/journal.pone.0190554

29. Robinson E, Titov N, Andrews G, McIntyre K, Schwencke G, Solley K. Internet treatment for generlized anxiety disorder: A randomized controlled trial comparing clinician vs. technician assistance. PLoS ONE. 2010;5(6). DOI: 10.1371/journal.pone.0010942

30. Titov N, Andrews G, Robinson E, Schwencke G, Johnston L, Solley K, et al. Clinician-assisted Internet-based treatment is effective for generalized anxiety disorder: Randomized controlled trial. Aust N Z J Psychiatry. 2009;43(10). DOI: 10.1080/00048670903179269

31. Brenes GA, Danhauer SC, Lyles MF, Hogan PE, Miller ME. Telephone-delivered cognitive behavioral therapy and telephone-delivered nondirective supportive therapy for rural older adults with generalized anxiety disorder: A randomized clinical trial. JAMA Psychiatry. 2015;72(10). DOI: 10.1001/jamapsychiatry.2015.1154

32. Brenes GA, Miller ME, Williamson JD, McCall WV, Knudson M, Stanley MA. A randomized controlled trial of telephone-delivered cognitive-behavioral therapy for late-life anxiety disorders. Am J Geriatr Psychiatry. 2012;20(8). DOI: 10.1097/JGP.0b013e31822ccd3e

3.2 Relaxation therapy

- ## Question

What is the comparative effectiveness and safety of relaxation therapy for adults diagnosed with GAD?

- ## Recommendations

EVIDENCE-BASED RECOMMENDATION

1. In patients with mild or moderate GAD whose symptoms have not improved after educational intervention including self-management of anxiety and advice on healthy lifestyles, relaxation therapy is suggested as an alternative to cognitive behavioural therapy. [Weak recommendation in favour]

- ## Rationale

A weak recommendation has been made in favour of the use of relaxation therapy as an alternative to CBT in patients with mild or moderate GAD whose symptoms have not improved after educational intervention.

The GUG has considered the magnitude of the expected beneficial effects and the benefit-risk balance.

Magnitude of the expected effects: The evidence indicates that relaxation therapy significantly reduces levels of anxiety, depression and worry and increases the likelihood of remission.

Benefit- Risk balance: Scientific evidence points to clear benefits of relaxation therapy in the treatment of GAD contributing to patient's general well-being, and to adverse events is considered negligible. The GUG has therefore concluded that the benefit-risk balance is globally favourable for this therapy.

It is important to bear in mind that results may vary between individuals and that relaxation therapy may not be suitable for all people or situations. In specific circumstances, a therapeutic approach that addresses symptoms or concerns more directly may be necessary. In the case of certain medical conditions, such as hypotension, it may be necessary to consider other therapeutic options. In such cases, it is essential to carefully assess the suitability of relaxation therapy and to explore alternatives that are better suited to the specific needs and circumstances of the patient. To do this, the person´s willingness and ability to participate, preferences, past experiences and contraindications should be considered before selecting a particular relaxation strategy and determining whether any relaxation intervention has been helpful in the past.

- ## Complete clinical question

Full information about this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-2

- **References**

1. Hoyer J, Becker ES, Margraf J. Generalized anxiety disorder and clinical worry episodes in young women. Psychol Med. 2002;32:1227-37. DOI: 10.1017/s0033291702006360

2. Barlow DH, Rapee RM, Brown TA. Behavioral treatment of generalized anxiety disorder. Behav Ther. 1992;23(4). DOI: 10.1016/S0005-7894(05)80221-7

3. Borkovec TD, Costello E. Efficacy of Applied Relaxation and Cognitive-Behavioral Therapy in the Treatment of Generalized Anxiety Disorder. J Consult Clin Psychol. 1993;61(4). DOI: 10.1037/0022-006X.61.4.611

4. Dugas MJ, Brillon P, Savard P, Turcotte J, Gaudet A, Ladouceur R, et al. A Randomized Clinical Trial of Cognitive-Behavioral Therapy and Applied Relaxation for Adults With Generalized Anxiety Disorder. Behav Ther. 2010;41(1). DOI: 10.1016/j.beth.2008.12.004

5. Conrad A, Isaac L, Roth WT. The psychophysiology of generalized anxiety disorder: 2. Effects of applied relaxation. Psychophysiology. 2008;45(3). DOI: 10.1111/j.1469-8986.2007.00644.x

6. Boletín Oficial del País Vasco. Osakidetza Servicio Vasco de Salud [Internet]. 2018 [citado 27 de octubre de 2022]. Disponible en: https://www.euskadi.eus/bopv2/datos/2018/02/1800712a.pdf

3.3 Metacognitive therapy

- **Question**

What is the comparative effectiveness and safety of metacognitive therapy in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. In patients with GAD, the use of metacognitive therapy is suggested as a second line of psychological treatment. [Weak recommendation in favour]

- **Rationale**

A weak recommendation has been made in favour of the use of metacognitive therapy in patients with GAD in the event that no respond is obtain with CBT or to relaxation therapy.

The working group has considered the magnitude of the expected beneficial effects, the benefit- risk balance and the feasibility application therapy.

Magnitude of the expected effects: scientific evidence indicates that metacognitive therapy has moderate to large effects on response and remission rates, and on levels of anxiety, quality of life and the management of worries.

Benefit- Risk balance: scientific evidence points to clear benefits of metacognitive therapy in the treatment of GAD and the possibility of adverse events associated with this therapy is considered negligible. Therefore, the GUG has considered that the benefit-risk balance

is globally favourable to metacognitive therapy. However, despite this positive benefit-risk balance there is less evidence available for this therapy than for CBT or relaxation therapy.

Feasibility: metacognitive therapy is not as widely used among professionals as CBT and relaxation therapy, which means that this therapy may not be generally feasible.

For all the above reasons, the GUG has considered leaving metacognitive therapy as a second line psychological treatment alternative for GAD. In any case, the decision will have to be assessed individually and on a personalised basis to determine the most appropriate option for each patient and their specific situation.

- ## Complete clinical question

Full information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-2

- ## References

1. Nordahl HM, Borkovec TD, Hagen R, Kennair LEO, Hjemdal O, Solem S, et al. Metacognitive therapy versus cognitive–behavioural therapy in adults with generalised anxiety disorder. BJPsych Open. 2018;4(5). DOI: 10.1192/bjo.2018.54

2. van der Heiden C, Muris P, van der Molen HT. Randomized controlled trial on the effectiveness of metacognitive therapy and intolerance-of-uncertainty therapy for generalized anxiety disorder. Behav Res Ther. 2012;50(2). DOI: 10.1016/j.brat.2011.12.005

3. Boletín Oficial del País Vasco. Osakidetza Servicio Vasco de Salud [Internet]. 2018 [citado 27 de octubre de 2022]. Disponible en: https://www.euskadi.eus/bopv2/datos/2018/02/1800712a.pdf

3.4 Acceptance and commitment therapy

- ## Question

What is the comparative effectiveness and safety of acceptance and commitment therapy, in adults with GAD?

- ## Recommendations

EVIDENCE-BASED RECOMMENDATION

1. In patients with GAD, it is suggested that acceptance and commitment therapy be used as a second line of psychological treatment. [Weak recommendation in favour]

- ## Rationale

A weak recommendation has been made in favour of the use of acceptance and commitment therapy in patients with GAD in the event that no response is obtained with CBT or with relaxation therapy. No evidence could be identified that directly compares the effects of metacognitive therapy with those of acceptance and commitment therapy for

patients with GAD. For this reason, the GUG has decided to recommend either therapy as a second line of psychological treatment, without prioritising one over the other.

The GUG has considered the magnitude of the expected beneficial effects and the benefit-risk balance.

Magnitude of expected effects: the evidence indicates that acceptance and commitment therapy has moderately positive effects on response and remission rates, anxiety levels and management of worries. None of the three studies considered reported results on adverse events.

Benefit -risk balance: due to the evidence of the benefits of acceptance and commitment therapy in the treatment of GAD and the possibility of adverse events associated with this therapy, which is considered negligible, the GUG has considered that the benefit- risk balance is globally favourable to acceptance and commitment therapy.

As CBT has a greater body of evidence than acceptance and commitment therapy, with proven benefits, the choice of acceptance and commitment therapy is suggested as a second line of psychological treatment. In any case, the decision will have to be assessed individually and personally to determine the most appropriate option for each patient and their specific situation.

- **Complete clinical question**

Full information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-2

- References

1. Zargar F, Farid AAA, Atef-Vahid MK, Afshar H, Maroofi M, Omranifard V. Effect of acceptance-based behavior therapy on severity of symptoms, worry and quality of life in women with generalized anxiety disorder. Iran J Psychiatry Behav Sci. 2012;6(2).

2. Roemer L, Orsillo SM, Salters-Pedneault K. Efficacy of an acceptance-based behavior therapy for generalized anxiety disorder: evaluation in a randomized controlled trial. J Consult Clin Psychol. diciembre de 2008;76(6):1083-9. DOI: 10.1037/a0012720

3. Dahlin M, Andersson G, Magnusson K, Johansson T, Sjögren J, Håkansson A, et al. Internet-delivered acceptance-based behaviour therapy for generalized anxiety disorder: A randomized controlled trial. Behav Res Ther. febrero de 2016;77:86-95. DOI: 10.1016/j.brat.2015.12.007

4. Boletín Oficial del País Vasco. Osakidetza Servicio Vasco de Salud [Internet]. 2018 [citado 27 de octubre de 2022]. Disponible en: https://www.euskadi.eus/bopv2/datos/2018/02/1800712a.pdf

3.5 Psychodynamic therapy

- **Question**

What is the comparative effectiveness and safety of psychodynamic therapy in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. In patients with GAD, it is suggested that psychodynamic therapy should not be applied [Weak recommendation against]

- **Rationale**

A weak recommendation has been made against the use of psychodynamic therapy in patients with GAD. The working group has considered the benefit-risk balance, the quality of the evidence and the costs.

Benefit-risk balance: psychodynamic therapy achieves similar results to CBT only when the patient has high contact (frequent) with the therapist, although the certainty of the evidence is low and limited.

Costs: psychodynamic therapy with a high level of contact with the therapist, involving between 16 and 20 sessions, would represent an increase in the costs of healthcare with respect to CBT.

Based on the above, the GUG has decided not to recommend this therapy in the treatment of GAD, as there are others with similar effects that have greater evidence and involve lower costs.

- **Complete clinical question**

Full information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-2

- **References**

1. Durham RC, Murphy T, Allan T, Richard K, Treliving LR, Fenton GW. Cognitive therapy, analytic psychotherapy and anxiety management training for generalised anxiety disorder. Br J Psychiatry. 1994;165(SEP.). DOI: 10.1192/bjp.165.3.315

2. Boletín Oficial del País Vasco. Osakidetza Servicio Vasco de Salud [Internet]. 2018 [citado 27 de octubre de 2022]. Disponible en: https://www.euskadi.eus/bopv2/datos/2018/02/1800712a.pdf

3. Health Quality Ontario. Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017;17(15):1-167.

3.6 Mindfulness

- **Question**

What is the comparative effectiveness and safety of mindfulness in adults with GAD?

• Recommendations

EVIDENCE-BASED RECOMMENDATION

1. Due to the low level of confidence in the available evidence, a recommendation cannot be made regarding the use of mindfulness for the treatment of people with GAD in Primary Care settings.

• Rationale

Although there are some preliminary studies suggesting that mindfulness may be beneficial in reducing anxiety in certain disorders, the scientific evidence is still limited and does not strongly support it as a main stream treatment for GAD. Research in this area is at its early stages and rigorous studies with larger sample sizes are needed to determine the effectiveness of mindfulness in this specific disorder.

GAD can present itself in a variety of ways in each individual and treatment varies from person to person. While mindfulness may be beneficial for some people as a complement to other therapeutic approaches, it may not be sufficient as a sole intervention to address the complex symptoms of GAD.

The GUG considers that, given the existence of effective treatment options available, solid evidence is required before recommending mindfulness as a mainstream alternative.

Finally, the group has based its decision on the current lack of regulation of mindfulness-based therapies and of adequate training of healthcare professionals to use them.

Overall certainty in the evidence on effects: the overall quality of the evidence considered is very low, coming from three RCTs (n= 308) with methodological limitations. The studies considered did not report the probability of response, probability of remission and rate of adverse effects.

Benefit- Risk balance: the group considers that benefit-risk balance of mindfulness is variable. This is due to the fact that the effects of mindfulness use on self-reported anxiety, worry and depression outcomes vary across the studies considered from very strong to effects of uncertain clinical significance.

• Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-2

• References

1. Hoge EA, Bui E, Marques L, Metcalf CA, Morris LK, Robinaugh DJ, et al. Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: Effects on anxiety and stress reactivity. J Clin Psychiatry. 2013;74(8). DOI: 10.4088/JCP.12m08083

2. Asmaee Majid S, Seghatoleslam T, Homan HA, Akhvast A, Habil H. Effect of mindfulness based stress management on reduction of generalized anxiety disorder. Iran J Public Health. 2012;41(10).

3. Wong SYS, Yip BHK, Mak WWS, Mercer S, Cheung EYL, Ling CYM, et al. Mindfulness-based cognitive therapy v. group psychoeducation for people with generalised anxiety disorder: Randomised controlled trial. Br J Psychiatry. 2016;209(1). DOI: 10.1192/bjp.bp.115.166124

4. Schlosser M, Sparby T, Vörös S, Jones R, Marchant NL. Unpleasant meditation-related experiences in regular meditators: Prevalence, predictors, and conceptual considerations. PLoS ONE. 2019;14(5). DOI: 10.1371/journal.pone.0216643

5. Cebolla A, Demarzo M, Martins P, Soler J, Garcia-Campayo J. Unwanted effects: Is there a negative side of meditation? A multicentre survey. PLOS ONE. 5 de septiembre de 2017;12(9):e0183137. DOI: 10.1371/journal.pone.0183137

6. Zargar F, Farid AAA, Atef-Vahid MK, Afshar H, Maroofi M, Omranifard V. Effect of acceptance-based behavior therapy on severity of symptoms, worry and quality of life in women with generalized anxiety disorder. Iran J Psychiatry Behav Sci. 2012;6(2).

7. Boletín Oficial del País Vasco. Osakidetza Servicio Vasco de Salud [Internet]. 2018 [citado 27 de octubre de 2022]. Disponible en: https://www.euskadi.eus/bopv2/datos/2018/02/1800712a.pdf

8. Zhang L, Lopes S, Lavelle T, Jones KO, Chen L, Jindal M, et al. Economic Evaluations of Mindfulness-Based Interventions: a Systematic Review. Mindfulness. octubre de 2022;13(10):2359-78. DOI: 10.1007/s12671-022-01960-1

4. Pharmacological treatment

4.1 Antidepressants

4.1.1 Selective serotonin reuptake inhibitors

- **Question**

What is the comparative effectiveness and safety of selective serotonin reuptake inhibitors (SSRIs) versus placebo, in adults with GAD?

- **Recommendations**

GOOD CLINICAL PRACTICE

1. In patients with severe GAD, the prescription of selective serotonin reuptake inhibitors is recommended, while assessment is still pending by the Mental Health Service.

EVIDENCE-BASED RECOMMENDATION

2. In patients with moderate GAD whose symptoms have not improved after educational intervention, including self-management of anxiety and advice on a healthy lifestyle, the choice of selective serotonin reuptake inhibitor is suggested as first line of pharmacological treatment. [Weak recommendation in favour].

GOOD CLINICAL PRACTICE

3. When prescribing antidepressants, the following should be considered: age, tolerance, potential side effects, the possibility of pregnancy, previous treatment received, the existence of comorbidities, potential risk of occasional overdose, potential interactions with other medications that are being received, concomitant consumption of toxic substances and the cost for equal effectiveness.

4. There is insufficient evidence to recommend one particular antidepressant over others. Therefore, it is suggested that the choice be made in a shared decision-making process between the patient and the healthcare professional, taking into account previous success with the individual patient, the patient's preference and the professional's judgement (including previous experience with the medication).

5. In order to reduce the likelihood and severity of side effects, it is suggested that treatment with antidepressants should be initiated at a low dose (approximately half the initial dose administered to patients with depression) and be titrated up gradually (increased according to tolerability, within the approved dose range) in order to achieve the desired therapeutic effect.

6. During pregnancy, the following should be considered:
   - Whether the potential benefits to the mother from the prescribed antidepressants outweigh the possible risks to the foetus.
   - Using the minimum effective dose of the drug and for the shortest possible time to reduce the potential risk of adverse neonatal effects.

7. When prescribing antidepressants for patients with GAD, it is recommended that detailed information be provided on:
    - The therapeutic objectives, duration of treatment and the risks of abrupt discontinuation of treatment.
    - The non-immediacy of the effect and the need for adherence to treatment.
    - The Potential adverse effects and to warn that these generally occur early in the treatment, even before the beneficial effects are noticed.

8. Initially, it is suggested to see the patient weekly to monitor adherence, adverse effects and to identify any worsening of symptoms until there is a response and the symptoms have stabilised.

9. When a selective serotonin reuptake inhibitor (SSRI) is effective in the treatment of a patient with GAD, but is not tolerated, switching to another SSRI is suggested, unless severe or class reactions have occurred. If the latter is also not tolerated, switching to a serotonin-norepinephrine reuptake inhibitor is suggested.
10. It is suggested that the initial response be reviewed after 4-6 weeks of treatment and that the dose not be increased before that period.

11. If remission of symptoms occurs within 4-6 weeks of starting treatment, it is suggested that treatment is continued for approximately 6 to 12 months and that progress is monitored.

12. Should a partial response to initial treatment be observed within 4-6 weeks of treatment initiation, assessment in increasing treatment dosage within the therapeutic range is suggested, whilst ensuring that progress is monitored.

13. When withdrawal of medication is indicated, it is recommended that it be done progressively, with a reduction in dose over a period of weeks or months.

14. If there is no response to the initial treatment within 4-6 weeks of starting treatment, after checking compliance, confirming the diagnosis and reassessing the existence of possible comorbidities, it is suggested that a change in treatment be considered, consisting of: adding psychological therapy and/or increasing the dose within the approved dose range, or switching to another drug with a different mechanism of action.

15. If symptoms deteriorate within 4-6 weeks of commencing treatment, a switch to an alternative drug with different mechanism of action is suggested.

- ## Rationale

A weak recommendation has been made in favour of using SSRIs as a first-line pharmacological treatment for patients with moderate GAD whose symptoms have not improved after educational intervention.

The GUG has carefully considered the magnitude of the expected beneficial effects, the quality of the evidence, the benefit-risk balance together with the cost of these drugs and the general acceptability of these drugs by patients.

In addition, a series of good practice recommendations have been formulated in relation to the implementation of these recommendations. These are the relevant clinical considerations for the strategy in case of severe GAD: the considerations for prescription,

the non-preference of individual drugs within the class and the dosage, considerations in the case of pregnancy, the information that should be offered to the patient, the alternative in the case of non-tolerance to the initial treatment, the strategy in the case of severe GAD, the monitoring of adherence and response, the continuation and finalisation of the treatment and, finally, the alternative to non-response, based on the experience in the clinical practice of the GUG and the recommendations of the current CPGs of high methodological quality on GAD.

Magnitude of the expected effects: the evidence indicates that SSRIs have significant effects in reducing anxiety levels, increasing the probability of response and the probability of remission, as well as increasing the level of quality of life.

Overall certainty in the evidence of effects: the overall quality of the evidence considered, from 15 RCTs (n= 5737), is moderate.

Benefit-risk balance: the scientific evidence points to clear benefits of SSRIs in the treatment of GAD.

On the other hand, although SSRIs are not free of side effects, these are well known and some can be reduced by lowering the starting dose and remaining vigilant, providing the patient with the necessary information to detect them early. Consequently, the GUG has considered that the benefit-risk balance is globally favourable to SSRIs.

Use of resources and costs: the cost of treatment with SSRIs, taking into account only the cost of the drugs, is considered negligible.

Acceptability: SSRIs have a well-established safety profile and are widely used in primary care, therefore there is a great deal of experience of their use. Consequently, from the GUG's perspective, the majority of patients, once informed of the pros and cons, would agree to treatment.

- ## Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-3

References

1. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113] [Internet]. NICE; 2011. Disponible en: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997

2. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12):1109-72. DOI: 10.1177/0004867418799453 DOI: 0004-8674

3. Rickels K, Zaninelli R, McCafferty J, Bellew K, Iyengar M, Sheehan D. Paroxetine Treatment of Generalized Anxiety Disorder: A Double-Blind, Placebo-Controlled Study. Am J Psychiatry. 2003;160(4):749-56. DOI: 10.1176/appi.ajp.160.4.749

4. Dahl AA, Ravindran A, Allgulander C, Kutcher SP, Austin C, Burt T. Sertraline in generalized anxiety disorder: Efficacy in treating the psychic and somatic anxiety factors. Acta Psychiatr Scand. 2005;111(6):429-35. DOI: 10.1111/j.1600-0447.2005.00529.x

5. Brawman-Mintzer O, Knapp RG, Rynn M, Carter RE, Rickels K. Sertraline treatment for generalized anxiety disorder: A randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2006;67(6):874-81. DOI: 10.4088/jcp.v67n0603

6. Allgulander C, Dahl AA, Austin C, Morris PLP, Sogaard JA, Fayyad R, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry. 2004;161(9):1642-9. DOI: 10.1176/appi.ajp.161.9.1642

7. Stein D, Ahokas A, Márquez M, Höschl C, Oh K, Jarema M, et al. Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study. J Clin Psychiatry. septiembre de 2014;75(4):362-8. DOI: 10.4088/JCP.13m08433

8. Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study. Depress Anxiety. 2004;19(4):234-40. DOI: 10.1002/da.10146

9. Baldwin DS, Huusom AKT, Mæhlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder. Br J Psychiatry. 2006;189(3):264-72. DOI: 10.1192/bjp.bp.105.012799

10. Pollack M, Zaninelli R, Goddard A, McCafferty J, Bellew K, Burnham, DBMK I. Paroxetine in the treatment of generalized anxiety disorder: Results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry. 2001;62(5):350-7. DOI: 10.4088/jcp.v62n0508

11. Bandelow B, Chouinard G, Bobes J, Ahokas A, Eggens I, Liu S, et al. Extended-release quetiapine fumarate (quetiapine XR): A once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo-and active-controlled study. Int J Neuropsychopharmacol. 2010;13(3):305-20. DOI: 10.1017/S1461145709990423

12. Merideth C, Cutler AJ, She F, Eriksson H. Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: A randomized, placebo controlled and active-controlled study. Vol. 27, International Clinical Psychopharmacology. 2012. p. 40-54. DOI: 10.1097/YIC.0b013e32834d9f49

13. Lenze EJ, Rollman BL, Shear MK, Dew MA, Pollock BG, Ciliberti C, et al. Escitalopram for older adults with generalized anxiety disorder: A randomized controlled trial. JAMA - J Am Med Assoc. 2009;301(3):295-303. DOI: 10.1001/jama.2008.977

14. Bose A, Korotzer A, Gommoll C, Li D. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of generalized anxiety disorder. Depress Anxiety. 2008;25(10):854-61. DOI: 10.1002/da.20355

15. Durgam S, Gommoll C, Forero G, Nunez R, Tang X, Mathews M, et al. Efficacy and Safety of Vilazodone in Patients With Generalized Anxiety Disorder. Vol. 77, The Journal of Clinical Psychiatry. 2016. p. 1687-94. DOI: 10.4088/JCP.15m09885

16. Gommoll C, Forero G, Mathews M, Nunez R, Tang X, Durgam S, et al. Vilazodone in patients with generalized anxiety disorder: A double-blind, randomized, placebo-controlled, flexible-dose study. Vol. 30, International Clinical Psychopharmacology. 2015. p. 297-306. DOI: 10.1097/YIC.0000000000000096

17. Gommoll C, Durgam S, Mathews M, Forero G, Nunez R, Tang X, et al. A double-blind, randomized, placebo-controlled, fixed-dose phase iii study of vilazodone in patients with generalized anxiety disorder. En: Depression and Anxiety. 2015. p. 451-9. DOI: 10.1002/da.22365

18. Mavranezouli I, Meader N, Cape J, Kendall T. The cost effectiveness of pharmacological treatments for generalized anxiety disorder. PharmacoEconomics. 2013;31(4):317-33. DOI: 10.1007/s40273-013-0031-z

19. Bosman RC, Huijbregts KM, Verhaak PF, Ruhé HG, van Marwijk HW, van Balkom AJ, et al. Long-term antidepressant use: a qualitative study on perspectives of patients and GPs

in primary care. Br J Gen Pract. octubre de 2016;66(651):e708-19. DOI: 10.3399/bjgp16X686641

4.1.2 Serotonin and noradrenaline reuptake inhibitors

• Question

What is the comparative effectiveness and safety of serotonin and noradrenaline reuptake inhibitors (SNRIs) compared to placebo, in adults with GAD?

• Recommendations

EVIDENCE-BASED RECOMMENDATION

1. Selective serotonin and noradrenaline reuptake inhibitors (venlafaxine extended-release and duloxetine) are suggested as first-line treatment for people with GAD as an alternative to selective serotonin reuptake inhibitors. [Weak recommendation in favour]

GOOD CLINICAL PRACTICE

2. If a selective serotonin and noradrenaline reuptake inhibitor is effective in patients with a diagnosis of GAD, but it is intolerable, a change to another selective serotonin and noradrenaline reuptake inhibitor is suggested. If the latter is also not tolerated, switching to a selective serotonin reuptake inhibitor is suggested.

The Good Clinical Practice (GCP) recommendations 3-8 and 10-13 that were formulated for selective serotonin reuptake inhibitors (see Section 6.1.1.) are also applicable to selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors.

• Rationale

A weak recommendation has been made in favour of using SNRIs as an alternative to SSRIs in patients with moderate GAD whose symptoms have not improved after educational intervention.

The recommendation has been based on the magnitude of the expected beneficial effects, the quality of the evidence, the favourable benefit-risk balance together with the low cost of these drugs and their general acceptability to patients.

In addition, a recommendation for good practice has formulated to complement these recommendations. This is intended to provide an alternative in the event of intolerance to the initial treatment. The set of GCP recommendations, that apply to both SSRIs and SNRIs, are considerations for prescription, non-preference of individual drugs within the class and dosage, considerations in the case of pregnancy, information to be given to the patient, strategy in case of severe GAD, monitoring of adherence and response, continuation and discontinuation of treatment and, finally, alternatives in the case of non-response. In doing so, the GUD has taken into account clinical experience with GAD and the recommendations of current, methodologically high-quality guidelines on GAD.

Magnitude of the expected effects is as follows: the evidence indicates that NRSIs have a significant effect in increasing the probability of response and the probability of remission and a small effect on anxiety levels and quality of life.

Overall certainty in the evidence of the effects: the overall quality of the evidence considered, from 19 RCTs (n= 7,809), is moderate.

Benefit-risk balance: the scientific evidence points to clear benefits of NSRIs in the treatment of GAD. On the other hand, although NSRIs are not free of side effects, these are well known and some can be reduced by lowering the starting dose and remaining vigilant, providing the patient with the necessary information to detect them early. Consequently, the GUG has considered that the benefit-risk balance is globally favourable for NSRIs.

Use of resources and costs: the cost of treatment with NSRIs, taking into account only the cost of the drugs, is considered negligible.

Acceptability: NSRIs have a well-established safety profile and are widely used in PC, so there is a great deal of experience of their use. Therefore, from the GUG's point of view, the majority of patients, once informed of the pros and cons, would agree to the treatment.

• Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-3

• References

1. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113] [Internet]. NICE; 2011. Disponible en: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997

2. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12):1109-72. DOI: 10.1177/0004867418799453 DOI: 0004-8674

3. Bose A, Korotzer A, Gommoll C, Li D. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of generalized anxiety disorder. Depress Anxiety. 2008;25(10):854-61. DOI: 10.1002/da.20355

4. Nicolini H, Bakish D, Duenas H, Spann M, Erickson J, Hallberg C, et al. Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: Examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial. Psychol Med. 2009;39(2):267-76. DOI: 10.1017/S0033291708003401

5. Hartford J, Kornstein S, Liebowitz M, Pigott T, Russell J, Detke M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: Results from a placebo and active-controlled trial. Int Clin Psychopharmacol. 2007;22(3):167-74. DOI: 10.1097/YIC.0b013e32807fb1b2

6. Alaka K, Noble W, Montejo A, Duenas H, Munshi A, Lenox-Smith A, et al. Efficacy and Safety of Duloxetine in the Treatment of Older Adult Patients With Generalized Anxiety Disorder: a Randomized, Double-Blind, Placebo-Controlled Trial. Int J Geriatr Psychiatry. 2014;29(9):978-86. DOI: 10.1002/gps.4088

7. Mahableshwarkar AR, Jacobsen PL, Serenko M, Chen Y. A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10mg in acute treatment of adults with generalized anxiety disorder. Hum Psychopharmacol. 2014;29:64-72. DOI: 10.1002/hup.2371

8. Kasper S, Herman B, Nivoli G, Ameringen MV, Petralia A, Mandel FS, et al. Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind. Int Clin Psychopharmacol. 2009;24(2):87-96. DOI: 10.1097/YIC.0b013e32831d7980

9. Allgulander C, Nutt D, Detke M, Erickson J, Spann M, Walker D, et al. A non-inferiority comparison of duloxetine and venlafaxine in the treatment of adult patients with generalized anxiety disorder. J Psychopharmacol (Oxf). 2008;22(4):417-25. DOI: 10.1177/0269881108091588

10. Rynn M, Russell J, Erickson J, Detke MJ, Ball S, Dinkel J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: A flexible-dose, progressive-titration, placebo-controlled trial. Depress Anxiety. 2008;25(3):182-9. DOI: 10.1002/da.20271

11. Hackett D, Haudiquet V, Salinas E. A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. Eur Psychiatry. 2003;18(4):182-7. DOI: 10.1016/s0924-9338(03)00046-4

12. Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: A 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. Vol. 67, Journal of Clinical Psychiatry. 2006. p. 771-82. DOI: 10.4088/JCP.v67n0511

13. Koponen H, Allgulander C, Erickson J, Dunayevich E, Pritchett Y, Detke MJ, et al. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. Prim Care Companion J Clin Psychiatry. 2007;9(2):100-7. DOI: 10.4088/pcc.v09n0203

14. Lenox-Smith AJ, Reynolds A. A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care. Br J Gen Pract J R Coll Gen Pract. 2003;53(495):772-7.

15. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br J Psychiatry J Ment Sci. julio de 2001;179:15-22. DOI: 10.1192/bjp.179.1.15

16. Gelenberg AJ, Lydiard RB, Rudolph RL, Aguiar L, Haskins JT, Salinas E. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: A 6-month randomized controlled trial. JAMA. junio de 2000;283(23):3082-8. DOI: 10.1001/jama.283.23.3082

17. Nimatoudis I, Zissis NP, Kogeorgos J, Theodoropoulou S, Vidalis A, Kaprinis G. Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder. A double-blind, randomized, placebo controlled study. Int Clin Psychopharmacol. noviembre de 2004;19(6):331-6. DOI: 10.1097/00004850-200411000-00003

18. Wu WY, Wang G, Ball SG, Desaiah D, Ang QQ. Duloxetine versus placebo in the treatment of patients with generalized anxiety disorder in China. Chin Med J (Engl). 2011;124(20):3260-8.

19. Davidson J, DuPont R, Hedges D, Haskins J. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry. 1999;60(8):528-35. DOI: 10.4088/jcp.v60n0805

20. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. J Clin Psychopharmacol. octubre de 2004;24(5):488-96. DOI: 10.1097/01.jcp.0000138764.31106.60

21. Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release Venlafaxine in nondepressed outpatients with generalized anxiety disorder. 2000.

22. Mahableshwarkar AR, Jacobsen PL, Chen Y, Simon JS. A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine

in the acute treatment of adults with generalised anxiety disorder. Int J Clin Pract. 2014;68(1):49-59. DOI: 10.1111/ijcp.12328

23. Mavranezouli I, Meader N, Cape J, Kendall T. The cost effectiveness of pharmacological treatments for generalized anxiety disorder. PharmacoEconomics. 2013;31(4):317-33. DOI: 10.1007/s40273-013-0031-z

Bosman RC, Huijbregts KM, Verhaak PF, Ruhé HG, van Marwijk HW, van Balkom AJ, et al. Long-term antidepressant use: a qualitative study on perspectives of patients and GPs in primary care. Br J Gen Pract. octubre de 2016;66(651):e708-19. DOI:

4.1.3 Other antidepressants

4.1.3.1 Agomelatine

- **Question**

What is the comparative effectiveness and safety of agomelatine versus placebo, in adults diagnosed with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. It is suggested not to use Antidepressant agomelatine for the treatment of people with GAD. [Weak recommendation against]

- **Rationale**

A weak recommendation has been formulated against the use of agomelatine in patients with GAD. The working group has considered the best available evidence of the effectiveness over other first-line antidepressants, safety considerations and the cost of the drug.

Magnitude of expected effects: the evidence indicates that agomelatine has a large effect on anxiety levels and a clinically significant effect on response and remission rates. However, SSRIs and SNRIs have more robust evidence base and have been shown to be effective in the treatment of GAD. These medications have well-established safety profiles and are more familiar to GPs.

Although agomelatine is generally considered to be well tolerated, it has certain safety considerations that should be taken into account. It may increase the risk of liver damage, so regular monitoring of liver function is required during treatment. In addition, it has significant drug interactions with other medications, which may limit its use in patients on multiple medications. These considerations may complicate its use in the PC setting, where monitoring and managing interactions may be more challenging.

Resource use and costs: the cost of agomelatine may be significantly higher compared to other more common antidepressants.

- **Complete clinical question**

Full information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-3

- **References**

1. Stein D, Ahokas A, Márquez M, Höschl C, Oh K, Jarema M, et al. Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study. J Clin Psychiatry. septiembre de 2014;75(4):362-8. DOI: 10.4088/JCP.13m08433

2. Stein DJ, Ahokas AA, De Bodinat C. Efficacy of agomelatine in generalized anxiety disorder: A randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008;28(5):561-6. DOI: 10.1097/JCP.0b013e318184ff5b

3. Stein DJ, Ahokas A, Jarema M, Avedisova AS, Vavrusova L, Chaban O, et al. Efficacy and safety of agomelatine (10 or 25 mg/day) in non-depressed out-patients with generalized anxiety disorder: A 12-week, double-blind, placebo-controlled study. Eur Neuropsychopharmacol. 2017;27(5):526-37. DOI: 10.1016/j.euroneuro.2017.02.007

4.1.3.2 Vortioxetine

- **Question**

What is the comparative effectiveness and safety of vortioxetine versus placebo, in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. It is suggested that the antidepressant vortioxetine should not be used in the treatment of people with GAD. [Weak recommendation against]

- **Rationale**

A weak recommendation against the use of vortioxetine in patients with GAD has been made. The working group has considered the benefit-risk balance and the non-negligible cost of the drug.

Benefit-risk balance: the scientific evidence does not indicate benefits of treatment with vortioxetine and it could be associated with the appearance of adverse events. Therefore, the GUG has considered that the benefit-risk balance is globally unfavourable to the use of this drug.

Use of resources and costs: the cost of vortioxetine is significantly higher than that of other more common antidepressants

- **Complete clinical question**

Full information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-3

- **References**

1. Mahableshwarkar AR, Jacobsen PL, Chen Y, Simon JS. A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder. Int J Clin Pract. 2014;68(1):49-59. DOI: 10.1111/ijcp.12328

2. Mahableshwarkar AR, Jacobsen PL, Serenko M, Chen Y. A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10mg in acute treatment of adults with generalized anxiety disorder. Hum Psychopharmacol. 2014;29:64-72. DOI: 10.1002/hup.2371

3. Bidzan L, Mahableshwarkar AR, Jacobsen P, Yan M, Sheehan DV. Vortioxetine (Lu AA21004) in generalized anxiety disorder: Results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. Eur Neuropsychopharmacol. 2012;22(12):847-57. DOI: 10.1016/j.euroneuro.2012.07.012

4. Rothschild AJ, Mahableshwarkar AR, Jacobsen P, Yan M, Sheehan DV. Vortioxetine (Lu AA21004) 5mg in generalized anxiety disorder: Results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States. Eur Neuropsychopharmacol. 2012;22(12):858-66. DOI: 10.1016/j.euroneuro.2012.07.011

4.2 Anxiolytics

4.2.1 Benzodiazepines

- **Question**

What is the comparative effectiveness and safety of benzodiazepines (BZD) versus placebo, in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. It is suggested that benzodiazepines should not be used to treat GAD, except as a short-term measure (limited to four weeks) during crises and only when rapid control of symptoms is crucial while waiting for a response to antidepressant and/or psychological treatment. [Weak recommendation against]

2. In cases where the use of benzodiazepines is deemed necessary for patients diagnosed with GAD, it is suggested that those with a long half-life be prescribed, given their reduced addictive potential. [Weak recommendation against]

3. It is suggested that benzodiazepines should not be used in elderly patients with GAD. [Weak recommendation against]

- **Rationale**

A weak recommendation has been made against the use of Benzodiazepines (BZDs) for the treatment of GAD. The GUG has considered the significant side effects, the high risk of developing tolerance, physical and psychological dependence and abuse, as well as

the withdrawal symptoms upon their discontinuation. They have also taken into account the availability of safer and more effective alternatives, and their low perceived benefit in clinical practice.

The recommendation for their exceptional use as a temporary, short-term solution in crisis situations and only when it is essential to provide rapid symptoms control until the therapeutic effect of antidepressants and/or psychological treatment takes effect, is justified by the rapid anxiolytic effect of BZDs and by the fact that, in some cases, it may take time to achieve an adequate therapeutic response with antidepressants and/or psychological treatment. In acute crisis situations, where symptoms are severe and debilitating, the use of BZDs may be necessary as a temporary measure to provide rapid control of symptoms and reduce patient discomfort while waiting for the main treatment to reach its full effectiveness.

By limiting the use of BZDs to a period of ≤4 weeks and only in crucial situations, the aim is to minimise the risks associated with their long-term use, such as dependence and adverse effects. It is essential that the use of BZDs is carefully supervised by a doctor, who will assess the potential benefit and weigh up the risks in each individual case. In addition, in general, it is recommended to prioritise the prescription of those BZDs with a longer half-life as they have a lower addictive potential. In addition, adequate adherence to the treatment plan, including its limitations, should be monitored in order to reduce the time and amount of BZD consumption. It is also important to bear in mind that this group of drugs is included in the PRISCUS list and the STOPP-START and Beers criteria (potentially inappropriate medication in the elderly) as it can produce serious adverse effects such as increased risk of falls, prolonged reaction time, cognitive impairment or depression in this population group.

It is important to inform and advise patients about the risks associated with the use of BZDs, about the short-term nature of treatment with them and the importance of following the comprehensive treatment plan to address GAD in the long term.

Overall certainty in the evidence on the effects: the overall quality of the evidence considered, from 21 RCTs (n= 2,193), is low. This is due to the fact that the studies present a certain inconsistency for some of the links considered that could not be explained by the established subgroup analyses (type of benzodiazepine and/or dose). The variables remission, concern, level of depression and quality of life were not reported in any of the studies.

Benefit-risk balance: due to the high risk of developing tolerance and physical and psychological dependence on BZDs, the GUG has considered that the benefits of treatment indicated by the scientific evidence in terms of reducing anxiety levels and increasing the likelihood of response probably do not outweigh the undesirable effects.

• Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-4

- **References**

1. O'Mahony D, Cherubini A, Guiteras AR, Denkinger M, Beuscart JB, Onder G, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. Eur Geriatr Med. 31 de mayo de 2023;14(4):625-32. DOI: 10.1007/s41999-023-00777-y

2. Power KG, Simpson RJ, Swanson V, Wallace LA, Feistner ATC, Sharp D. A controlled comparison of cognitive- behaviour therapy, Diazepam, and placebo, alone and in combination, for the treatment of generalised anxiety disorder. J Anxiety Disord. 1990;4(4). DOI: 10.1016/0887-6185(90)90026-6

3. Hackett D, Haudiquet V, Salinas E. A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. Eur Psychiatry. 2003;18(4):182-7. DOI: 10.1016/s0924-9338(03)00046-4

4. Rickels K, DeMartinis N, Aufdembrinke B. A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder. J Clin Psychopharmacol. 2000;20(1):12-8. DOI: 10.1097/00004714-200002000-00004

5. Brown GG, Ostrowitzki S, Stein MB, von Kienlin M, Liu TT, Simmons A, et al. Temporal profile of brain response to alprazolam in patients with generalized anxiety disorder. Psychiatry Res - Neuroimaging. 2015;233(3):394-401. DOI: 10.1016/j.pscychresns.2015.06.016

6. McLeod D, Hoehn-Saric R, Porges S, Zimmerli W. Effects of alprazolam and imipramine on parasympathetic cardiac control in patients with generalized anxiety disorder. Psychopharmacology (Berl). 1992;107(4):535-40. DOI: 10.1007/BF02245268

7. Rickels K, Schweizer E, DeMartinis N, Mandos L, Mercer C. Gepirone and diazepam in generalized anxiety disorder: a placebo-controlled trial. J Clin Psychopharmacol. 1997;17(4):272-7. DOI: 10.1097/00004714-199708000-00006

8. Cutler N, Sramek J, Keppel Hesselink J, Krol A, Roeschen J, Rickels K, et al. A double-blind, placebo-controlled study comparing the efficacy and safety of ipsapirone versus lorazepam in patients with generalized anxiety disorder: A prospective multicenter trial. J Clin Psychopharmacol. 1993;13(6):429-37. DOI: 10.1097/00004714-199312000-00009

9. Enkelmann R. Alprazolam versus buspirone in the treatment of outpatients with generalized anxiety disorder. Psychopharmacology (Berl). 1991;105:428. DOI: 10.1007/BF02244440

10. Fontaine R, Mercier P, Beaudry P, Annable L, Chouinard G. Bromazepam and lorazepam in generalized anxiety: a placebo-controlled study with measurement of drug plasma concentrations. Acta Psychiatr Scand. 1986;74(5):451-8. DOI: 10.1111/j.1600-0447.1986.tb06268.x

11. Fontaine R, Annable L, Chouinard G, Ogilvie R. Bromazepam and Diazepam in Generalized Anxiety. J Clin Psychopharmacol. 1983;3(2):80-7. DOI: 10.1097/00004714-198304000-00005

12. Kragh-Sorensen P, P. Holm, C. Fynboe, E. Schaumburg, B. Andersen, P. Bech, et al. Bromazepam in generalized anxiety - Randomized, multi-practice comparisons with both chlorprothixene and placebo. Psychopharmacology (Berl). 1990;100(3):383-6. DOI: 10.1007/BF02244611

13. Pecknold J, Matas M, Howarth B, Ross C, Swinson R, Vezeau C, et al. Evaluation of buspirone as an antianxiety agent: Buspirone and diazepam versus placebo. Can J Psychiatry. 1989;34(8):766-71. DOI: 10.1177/070674378903400804

14. Fontaine R, Beaudry P, Beauclair L, Chouinard G. Comparison of withdrawal of buspirone and diazepam: a placebo controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 1987;11(2-3):189-97. DOI: 10.1016/0278-5846(87)90059-5

15. Möller HJ, Volz HP, Reimann IW, Stoll KD. Opipramol for the treatment of generalized anxiety disorder: A placebo-controlled trial including an alprazolam-treated group. J Clin Psychopharmacol. 2001;21(1):59-65. DOI: 10.1097/00004714-200102000-00011

16. Rickels K, Pollack MH, Feltner DE, Lydiard RB, Zimbroff DL, Bielski RJ, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry. 2005;62(9):1022-30. DOI: 10.1001/archpsyc.62.9.1022

17. Pourmotabbed T, Mcleod DR, Hoehn-Saric R, Hipsley P, Greenblatt DJ. Treatment, Discontinuation, and Psychomotor Effects of Diazepam in Women With Generalized Anxiety Disorder. J Clin Psychopharmacol. 1996;16(3):202-7. DOI: 10.1097/00004714-199606000-00002

18. Ross C, Matas M. A clinical trial of buspirone and diazepam in the treatment of generalized anxiety disorder. Can J Psychiatry. 1987;32(5):351-5. DOI: 10.1177/070674378703200505

19. Feltner D, Crockatt J, Dubovsky S, Cohn C, Shrivastava R, Targum S, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol. 2003;23(3):240-9. DOI: 10.1097/01.jcp.0000084032.22282.ff

20. Fresquet A, Sust M, Lloret A, Murphy MF, Carter FJ, Campbell GM, et al. Efficacy and safety of lesopitron in outpatients with generalized anxiety disorder. Ann Pharmacother. 2000;34(2):147-53. DOI: 10.1345/aph.19041

21. Pande AC, Crockatt JG, Feltner DE, Janney C a, Smith WT, Weisler R, et al. Pregabalin in Generalized Anxiety Disorder: A Placebo-Controlled Trial. Am J Psychiatry. 2003;160:533-40. DOI: 10.1176/appi.ajp.160.3.533

22. Ansseau M, Olié JP, von Frenckell R, Jourdain G, Stehle B, Guillet P. Controlled comparison of the efficacy and safety of four doses of suriclone, diazepam, and placebo in generalized anxiety disorder. Psychopharmacology (Berl). 1991;104:439-43. DOI: 10.1007/BF02245646

23. Schmitt R, Gazalle FK, Lima MSD, Cunha A, Souza J, Kapczinski F, et al. The efficacy of antidepressants for generalized anxiety disorder : a systematic review and meta-analyse. Rev Bras Psiquiatr. 2005;27(1516-4446 (Print)):18-24. DOI: 10.1590/S0101-81082009000300007

24. Crowe SF, Stranks EK. The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis. Arch Clin Neuropsychol. 1 de noviembre de 2018;33(7):901-11. DOI: 10.1093/arclin/acx120

25. Dubovsky SL, Marshall D. Benzodiazepines Remain Important Therapeutic Options in Psychiatric Practice. Psychother Psychosom. 2022;91(5):307-34. DOI: 10.1159/000524400

26. Edinoff AN, Nix CA, Hollier J, Sagrera CE, Delacroix BM, Abubakar T, et al. Benzodiazepines: Uses, Dangers, and Clinical Considerations. Neurol Int. 10 de noviembre de 2021;13(4):594-607. DOI: 10.3390/neurolint13040059

27. Cook JM, Marshall R, Masci C, Coyne JC. Physicians' Perspectives on Prescribing Benzodiazepines for Older Adults: A Qualitative Study. J Gen Intern Med. marzo de 2007;22(3):303-7. DOI: 10.1007/s11606-006-0021-3

4.2.2 Other anxiolytics

4.2.2.1 Buspirone

- ## Question

What is the comparative effectiveness and safety of buspirone versus placebo, in adults with GAD?

- ## Recommendations

EVIDENCE-BASED RECOMMENDATION

1. It is suggested not to use buspirone for the treatment of people with GAD. [Weak recommendation against]

- ## Rationale

A weak recommendation has been made against the use of buspirone in patients with GAD. The GUG has taken into account the unfavourable benefit-risk balance of this drug together with the fact that it is not marketed in Spain.

Benefit-risk balance: Scientific evidence does not indicate benefits of buspirone in the treatment of GAD over placebo in terms of anxiety levels, likelihood of response and rate of adverse events; however, the certainty of these effects was rated as very low. The variables remission, worry, level of depression and quality of life were not reported in any of the studies considered. Therefore, the GUG has considered that the balance between desirable and undesirable effects does not favour buspirone.

In terms of feasibility, Buspirone is not applicable to this context since it is not marketed in Spain.

- ## Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-4

- ## References

28. Davidson J, DuPont R, Hedges D, Haskins J. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry. 1999;60(8):528-35. DOI: 10.4088/jcp.v60n0805

29. Enkelmann R. Alprazolam versus buspirone in the treatment of outpatients with generalized anxiety disorder. Psychopharmacology (Berl). 1991;105:428. DOI: 10.1007/BF02244440

30. Pecknold J, Matas M, Howarth B, Ross C, Swinson R, Vezeau C, et al. Evaluation of buspirone as an antianxiety agent: Buspirone and diazepam versus placebo. Can J Psychiatry. 1989;34(8):766-71. DOI: 10.1177/070674378903400804

31. Fontaine R, Beaudry P, Beauclair L, Chouinard G. Comparison of withdrawal of buspirone and diazepam: a placebo controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 1987;11(2-3):189-97. DOI: 10.1016/0278-5846(87)90059-5

32. Ross C, Matas M. A clinical trial of buspirone and diazepam in the treatment of generalized anxiety disorder. Can J Psychiatry. 1987;32(5):351-5. DOI: 10.1177/070674378703200505

33. Delle Chiaie R, Pancheri P, Casacchia M, Stratta P, Kotzalidis GD, Zibellini M. Assessment of the efficacy of buspirone in patients affected by generalized anxiety disorder, shifting to buspirone from prior treatment with lorazepam: a placebo-controlled, double-blind study. J Clin Psychopharmacol. febrero de 1995;15(1):12-9. DOI: 10.1097/00004714-199502000-00003

34. Lader M, Scotto JC. A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. Psychopharmacology (Berl). octubre de 1998;139(4):402-6. DOI: 10.1007/s002130050731

4.3 Other drugs

4.3.1 Pregabalin

- **Question**

In adults with GAD, what is the comparative effectiveness and safety of pregabalin versus placebo?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. If the person with GAD does not tolerate selective serotonin reuptake inhibitors or selective serotonin and noradrenaline reuptake inhibitors, it is suggested that pregabalin be offered as a second line treatment, especially in those with neuropathic pain. [Weak recommendation in favour]

GOOD CLINICAL PRACTICE

2. It is suggested that the prescription of pregabalin should be avoided in patients with a history of or high risk of substance abuse.

- **Rationale**

A weak recommendation has been made in favour of the use of pregabalin in patients with GAD who do not tolerate SSRIs and SNRIs. The working group has considered the overall quality of the evidence and the benefit-risk balance. On the other hand, it considered that, due to its unique mechanism of action, pregabalin may be useful for those who do not tolerate SSRIs and SNRIs. It was also considered that misuse of pregabalin may lead to dependence and motivate behaviours of abuse and illegal trafficking, particularly in patients with a history of drug addiction.

Overall certainty of the evidence on effects the overall quality of the evidence considered, from 6 RCTs (n= 1,667), is moderate. The variables probability of remission and level of concern were not reported in any of the studies.

Benefit-risk balance: According to the results, the use of pregabalin is beneficial in the treatment of GAD with respect to anxiety levels and the likelihood of response, without increasing the risk of serious adverse events. Therefore, the GUG has considered that the benefit-risk balance is overall favourable to this medicine.

Pregabalin is indicated in the product´s data sheet for the treatment of peripheral and central neuropathic pain in adults, and the group considers that the use of this medicine in these patients may provide a dual benefit, avoiding duplication in the overall treatment of patients with GAD and neuropathic pain.

Pregabalin has a low addictive potential at therapeutic doses but on occasions it can be consumed at higher than recommended doses or by non-recommended routes of administration, to produce sedative and psychedelic effects. This misuse can lead to dependence and encourage abuse and trafficking, particularly in patients with a history of drug dependence. For this reason, a good practice recommendation has been made to avoid their use in patients with a history of, or high risk of. Substance misuse.

- ## Complete clinical question

Full information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-5

- ## References

35. Kasper S, Herman B, Nivoli G, Ameringen MV, Petralia A, Mandel FS, et al. Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind. Int Clin Psychopharmacol. 2009;24(2):87-96. DOI: 10.1097/YIC.0b013e32831d7980

36. Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: A 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. Vol. 67, Journal of Clinical Psychiatry. 2006. p. 771-82. DOI: 10.4088/JCP.v67n0511

37. Rickels K, Pollack MH, Feltner DE, Lydiard RB, Zimbroff DL, Bielski RJ, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry. 2005;62(9):1022-30. DOI: 10.1001/archpsyc.62.9.1022

38. Feltner D, Crockatt J, Dubovsky S, Cohn C, Shrivastava R, Targum S, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol. 2003;23(3):240-9. DOI: 10.1097/01.jcp.0000084032.22282.ff

39. Pande AC, Crockatt JG, Feltner DE, Janney C a, Smith WT, Weisler R, et al. Pregabalin in Generalized Anxiety Disorder: A Placebo-Controlled Trial. Am J Psychiatry. 2003;160:533-40. DOI: 10.1176/appi.ajp.160.3.533

40. Pohl RB, Feltner DE, Fieve RR, Pande AC. Efficacy of pregabalin in the treatment of generalized anxiety disorder: Double-blind, placebo-controlled comparison of BID versus TID dosing. J Clin Psychopharmacol. 2005;25(2):151-8. DOI: 10.1097/01.jcp.0000155820.74832.b0

41. Mavranezouli I, Meader N, Cape J, Kendall T. The cost effectiveness of pharmacological treatments for generalized anxiety disorder. PharmacoEconomics. 2013;31(4):317-33. DOI: 10.1007/s40273-013-0031-z

4.3.2 Quetiapine

- ## Question

What is the comparative effectiveness and safety of quetiapine versus placebo in adults with GAD?

- ## Recommendations

EVIDENCE-BASED RECOMMENDATION

1. In people with refractory GAD with high anxiety and at risk of benzodiazepine abuse or cognitive impairment, the use of quetiapine is suggested as an alternative to benzodiazepines [Weak recommendation]

GOOD CLINICAL PRACTICE

2. In the context of PC settings, it is suggested that the dose of quetiapine should not exceed 50 mg/d, with referral to the Mental Health Service if the patient cannot be controlled with these doses.

- ## Rationale

A weak recommendation has been made in favour of the use of quetiapine as an alternative to BZD in patients with GAD at risk of BZD abuse or cognitive impairment. The working group has considered the quality of the evidence and the benefit-risk balance.

Moreover, to complement this recommendation, a good practice recommendation has been made on the maximum dose of quetiapine to be used in PC, based on the fact that it is a drug with an antipsychotic effect and with a potential risk of serious adverse effects as well as multiple drug interactions. It therefore requires close monitoring by doctors who are experts in its use. At low doses, it has no antipsychotic effect and the side effects are reduced.

Overall certainty in the evidence on the effects: the overall quality of the evidence considered, from 3 RCTs (n= 1,706), is high. The variable level of concern was not reported in any of the studies.

Risk-benefit balance: the scientific evidence points to benefits of quetiapine in the treatment of GAD, with improvement in the level of anxiety and the likelihood of response and remission, however, it also points to an increased risk of adverse events.

The GUG has considered that the use of quetiapine may be useful in PC in those patients at risk of substance abuse or cognitive impairment, as an alternative to BZD and at low doses, since, in these cases, the beneficial effects outweigh the risks.

- ## Complete clinical question

Please, find complete information on the clinical question (available in Spanish)

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-5

- **References**

42. Bandelow B, Chouinard G, Bobes J, Ahokas A, Eggens I, Liu S, et al. Extended-release quetiapine fumarate (quetiapine XR): A once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo-and active-controlled study. Int J Neuropsychopharmacol. 2010;13(3):305-20. DOI: 10.1017/S1461145709990423

43. Khan A, Joyce M, Atkinson S, Eggens I, Baldytcheva I, Eriksson H. A randomized, double-blind study of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalized anxiety disorder. J Clin Psychopharmacol. agosto de 2011;31(4):418-28. DOI: 10.1097/JCP.0b013e318224864d

44. Merideth C, Cutler AJ, She F, Eriksson H. Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: A randomized, placebo controlled and active-controlled study. Vol. 27, International Clinical Psychopharmacology. 2012. p. 40-54. DOI: 10.1097/YIC.0b013e32834d9f49

45. CIMA - Ficha técnica Quetiapina 25 mg [Internet]. [citado 29 de junio de 2023]. Disponible en: https://cima.aemps.es/cima/dochtml/ft/69805

4.3.3 Opipramol

- **Question**

In adults with GAD, what is the comparative effectiveness and safety of opipramol versus placebo?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. Opipramol is not recommended at PC for the treatment of people diagnosed with GAD. [Weak recommendation against]

- **Rationale**

A weak recommendation has been made against the use of opipramol in patients with GAD based on the available evidence, which is scarce and of very low quality both in terms of the risks and benefits of treatment in these patients, together with the non-commercialisation of the drug in Spain.

Overall certainty in the evidence about the effects: the evidence considered comes from a single RCT (n= 208) which is imprecise in the only two outcomes reported (level of anxiety and rate of adverse events). Therefore, the overall quality of the evidence is considered very low.

Feasibility: treatment with opipramol is not applicable in this context as it is not marketed in Spain.

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-5

- ## References

46. Möller HJ, Volz HP, Reimann IW, Stoll KD. Opipramol for the treatment of generalized anxiety disorder: A placebo-controlled trial including an alprazolam-treated group. J Clin Psychopharmacol. 2001;21(1):59-65. DOI: 10.1097/00004714-200102000-00011

5. Other treatments

5.1 Physical exercise programmes

- **Question**

In adults with GAD, what is the comparative effectiveness and safety of resistance exercise programmes compared to control?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. It is suggested that people with GAD be recommended to regularly participate in a supervised physical exercise programme as a complement to the prescribed psychological and/or pharmacological treatment. [Weak recommendation in favour]

Considerations for implementation:

It is vital that physical exercise programmes should be adapted to meet the specific needs of patients diagnosed with GAD.

Before starting any exercise programme, it is recommended that consulting a certified personal trainer or a health professional specialized in therapeutic exercise be made to ensure the safety and adequacy of physical activity to the specific physical and mental conditions of each person.

As recommended by the WHO for the entire adult population, patients should engage in at least 150 to 300 minutes of moderate-intensity aerobic physical activity, or at least 75 to 150 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity throughout the week.

- **Rationale**

A weak recommendation has been made in favour of regular supervised physical exercise for patients with GAD. The GUG has considered that, based on indirect evidence from other populations, the benefits of regular supervised physical exercise probably outweigh the possible harms.

Benefit-risk balance: despite the limited evidence available on its specific effects on GAD, the GDG has considered that, the regular physical exercise can be an effective, as well as safe, tool to help people with GAD manage their symptoms and improve their mood and general well-being. This is based on the following benefits demonstrated in the general population and in people with other anxiety disorders and other mental disorders:

a) Reduction of anxiety and stress levels: During exercise, the body releases endorphins, neurotransmitters that generate a feeling of well-being and reduce anxiety. In addition, exercise can provide an effective distraction from negative thoughts and worries, thus promoting a calmer state of mind.

b) Improved mood: physical exercise can increase the production of serotonin and dopamine, brain chemicals related to mood and feelings of happiness. These chemical changes can have a positive effect on people with GAD, relieving the depressive symptoms that are often associated with the disorder.

c) Reduction of muscle tension: Generalised anxiety can cause muscle tension and stiffness, which can increase discomfort. Regular physical exercise, especially stretching and yoga, can help relax the muscles and relieve accumulated tension, which in turn can reduce the physical symptoms associated with anxiety.

d) Increased confidence and self-esteem: Participating in a physical exercise programme can help people with GAD develop greater confidence in their physical abilities and capacities. Achieving exercise goals, improving endurance and strength, and seeing improvements in physical performance can increase self-esteem and the feeling of control over one's body and soul.

e) Improved sleep: GAD is often associated with difficulties in falling asleep and maintaining restful sleep. Regular physical exercise can promote better rest and quality of sleep. Additionally, exercising early in the day can assist in regulating the circadian rhythm, thereby facilitating night time sleep.

- ## Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-6

- ## References

1. Stubbs B, Vancampfort D, Hallgren M, Firth J, Veronese N, Solmi M, et al. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). Eur Psychiatry J Assoc Eur Psychiatr. octubre de 2018;54:124-44. DOI: 10.1016/j.eurpsy.2018.07.004
2. Heissel A, Heinen D, Leonie-Brokmeier L, Skarabis N, Kangas M, Vancampfort D, et al. Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression. Br J Sports Med. 1 de febrero de 2023;bjsports-2022-106282. DOI: 10.1136/bjsports-2022-106282
3. Chong TWH, Kootar S, Wilding H, Berriman S, Curran E, Cox KL, et al. Exercise interventions to reduce anxiety in mid-life and late-life anxiety disorders and subthreshold anxiety disorder: a systematic review. Ther Adv Psychopharmacol [Internet]. enero de 2022 [citado 22 de agosto de 2024];12. Disponible en: http://journals.sagepub.com/doi/10.1177/20451253221104958DOI: 10.1177/20451253221104958
4. Herring MP, Jacob ML, Suveg C, Dishman RK, O'Connor PJ. Feasibility of exercise training for the short-term treatment of generalized anxiety disorder: A randomized controlled trial. Psychother Psychosom. 2012;81(1). DOI: 10.1159/000327898
5. Barić H, Đorđević V, Cerovečki I, Trkulja V. Complementary and Alternative Medicine Treatments for Generalized Anxiety Disorder: Systematic Review and Meta-

analysis of Randomized Controlled Trials. Adv Ther. 2018;35(3):261-88. DOI: 10.1007/s12325-018-0680-6
6. World Health Organization. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Geneva; 2023.
7. Martland R, Mondelli V, Gaughran F, Stubbs B. Can high intensity interval training improve health outcomes among people with mental illness? A systematic review and preliminary meta-analysis of intervention studies across a range of mental illnesses. Vol. 263, Journal of Affective Disorders. 2020. DOI: 10.1016/j.jad.2019.11.039

5.2 Medicinal herbs

5.2.1 Chamomile

- **Question**

In adults with GAD, what is the comparative effectiveness and safety of chamomile extract versus placebo?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. It is suggested that people with GAD be recommended to consume chamomile as a complement to the prescribed psychological and/or pharmacological treatment. [Weak recommendation in favour]

- **Rationale**

A weak recommendation has been made in favour of the use of chamomile extract only as an adjuvant in the treatment of GAD despite the fact that the available evidence is on its effects as an individual treatment compared to placebo. The GDG has considered the benefit-risk balance and the cost of the product.

Benefit-risk balance: the evidence indicates some benefit of chamomile on anxiety levels in people with GAD. However, it should not be considered as an individual or main treatment because the evidence is very limited and there is variability in the response,

The GUG considered that, given the known potential digestive and sedative effects of chamomile, it could help to alleviate the symptoms that accompany GAD. On the other hand, the possibility of adverse events associated with this medicinal herb is considered negligible, the GUG has considered that the benefit-risk balance is globally favourable to chamomile.

Use of resources and costs: as it is a non-funded product, the cost of this treatment would be assumed entirely by the patient. However, given the low cost of this product, the GUG considers that the recommendation of its use would probably not have an impact on equity·

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- **References**

47. Mao JJ, Xie SX, Keefe JR, Soeller I, Li QS, Amsterdam JD. Long-term chamomile (Matricaria chamomilla L.) treatment for generalized anxiety disorder: A randomized clinical trial. Phytomedicine. 2016;23(14). DOI: 10.1016/j.phymed.2016.10.012

48. Amsterdam JD, Li Y, Soeller I, Rockwell K, Mao JJ, Shults J. A randomized, double-blind, placebo-controlled trial of oral matricaria recutita (chamomile) extract therapy for generalized anxiety disorder. J Clin Psychopharmacol. agosto de 2009;29(4):378-82. DOI: 10.1097/JCP.0b013e3181ac935c

49. Viola H, Wasowski C, Levi de Stein M, Wolfman C, Silveira R, Dajas F, et al. Apigenin, a component of Matricaria recutita flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. Planta Med. junio de 1995;61(3):213-6. DOI: 10.1055/s-2006-958058

50. Avallone R, Zanoli P, Puia G, Kleinschnitz M, Schreier P, Baraldi M. Pharmacological profile of apigenin, a flavonoid isolated from Matricaria chamomilla. Biochem Pharmacol. 1 de junio de 2000;59(11):1387-94. DOI: 10.1016/s0006-2952(00)00264-1

51. Hieu TH, Dibas M, Surya Dila KA, Sherif NA, Hashmi MU, Mahmoud M, et al. Therapeutic efficacy and safety of chamomile for state anxiety, generalized anxiety disorder, insomnia, and sleep quality: A systematic review and meta-analysis of randomized trials and quasi-randomized trials. Phytother Res PTR. junio de 2019;33(6):1604-15. DOI: 10.1002/ptr.6349

5.2.2 Passionflower

- **Question**

What is the comparative effectiveness and safety of passionflower extract versus oxazepam, in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. Due to the low confidence in the available evidence, a recommendation cannot be made on the use of passionflower to improve the symptoms of people with GAD.

- **Rationale**

The GUG has decided not to issue a recommendation either for or against the use of passion flower extract in patients with GAD, taking into account the magnitude of the expected effects, the quality of the evidence and the benefit-risk balance.

Magnitude of the expected effects: the evidence indicates that treatment with passion flower extract does not modify anxiety levels compared to oxazepam.

Overall certainty in the evidence on the effects: the overall quality of the evidence considered, from a single RCT with 36 participants, is very low due to the small sample size and the risk of bias due to selective reporting of results. Change in anxiety levels was the only key outcome reported in the study.

Benefit-risk balance: no benefit is observed in treatment with passionflower extract compared to oxazepam and there is no evidence on the expected undesirable effects, therefore the benefit-risk balance is unknown.

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- **References**

52. Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther. 2001;26(5):363-7. DOI: 10.1046/j.1365-2710.2001.00367.x

5.2.3 Valerian

- **Question**

In adults with GAD, what is the comparative effectiveness and safety of valerian extract versus diazepam and placebo?

- **Recommendation**

EVIDENCE-BASED RECOMMENDATION

1. Based on the available evidence, no recommendation can be made regarding the use of valerian to improve the symptoms of people with GAD.

- **Rationale**

The GUG has decided not to issue a recommendation for or against the use of valerian extract in patients with GAD, considering the magnitude of the expected effects, the quality of the evidence and the benefit-risk balance.

Magnitude of the expected effects: the evidence indicates that treatment with valerian extract does not modify anxiety levels compared to diazepam or placebo.

Overall certainty in the evidence of effects: the overall quality of the evidence considered, from a single RCT with 36 participants, is low due to the small sample size and the possible risk of bias given the insufficient information in the domains of allocation concealment and incomplete outcome data. The variation in the anxiety levels was the only key outcome reported in the study.

Benefit-risk balance: no benefit is observed in treatment with valerian extract compared to diazepam or placebo and there is no evidence on the expected undesirable effects, therefore the benefit-risk balance is unknown.

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- **References**

53. Andreatini R, Sartori VA, Seabra MLV, Leite JR. Effect of valepotriates (valerian extract) in generalized anxiety disorder: A randomized placebo-controlled pilot study. Phytother Res. 2002;16(7). DOI: 10.1002/ptr.1027

5.2.4 Galphimia Glauca or red arnica

- **Question**

What is the comparative effectiveness and safety of galphimia glauca versus lorazepam, in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. Due to the low confidence in the available evidence, a recommendation cannot be made on the consumption of galphimia glauca (root arnica or red arnica) to improve the symptoms of people with GAD.

- **Rationale**

The GUG has decided not to make a recommendation for or against the use of galphimia glauca in patients with GAD, based on the quality of the evidence and the benefit-risk balance.

Overall certainty in the evidence about the effects: the overall quality of the evidence considered, from two RCTs (n=223), is very low due to the possible risk of bias given the insufficient information in the domains of participant selection and participants reported outcomes in both studies and the high risk of attrition bias in one of the included studies. The change in anxiety levels was the only key outcome reported in that study.

Benefit-risk balance: the evidence indicates that treatment with galphimia glauca does not modify anxiety levels compared to lorazepam and there is no evidence on the expected undesirable effects, therefore the benefit-risk balance is unknown.

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- **References**

54. Herrera-Arellano A, Jiménez-Ferrer E, Zamilpa A, Morales-Valdéz M, García-Valencia CE, Tortoriello García J. Efficacy and tolerability of a standardized herbal product from Galphimia glauca on generalized anxiety disorder. A randomized, double-blind clinical trial controlled with lorazepam. Planta Med. 2007;73(8). DOI: 10.1055/s-2007-981539

55. Herrera-Arellano A, Jiménez-Ferrer JE, Zamilpa A, García-Alonso G, Herrera-Alvarez S, Tortoriello J. Therapeutic Effectiveness of Galphimia glauca vs. Lorazepam in Generalized Anxiety Disorder. A Controlled 15-Week Clinical Trial. Planta Med. 2012;78:1529-35. DOI: 10.1055/s-0032-1315110

5.2.5 Kava

- **Question**

In adults with GAD, what is the comparative effectiveness and safety of kava versus placebo?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. Due to the low confidence in the available evidence, a recommendation cannot be made on the use of kava to improve the symptoms of people with GAD.

- **Rationale**

The GUG has decided not to issue a recommendation for or against the use of kava in patients with GAD, considering the magnitude of the expected effects, the quality of the evidence and the benefit-risk balance.

Magnitude of expected effects: the evidence indicates that treatment with kava neither modify the anxiety levels nor the response rate compared to placebo.

Overall certainty in the evidence of effects: the overall quality of the evidence, from 3 RCTs (n= 130) with methodological limitations, was considered low due to the small sample size and the presence of risk of bias in the studies due to the absence of a washout period. The variables probability of remission and level of worry were not reported in any of the studies.

Benefit-risk balance: no benefit is observed in treatment with kava compared to placebo and there is no evidence on the expected undesirable effects, therefore the benefit-risk balance is unknown.

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- **References**

1. Connor KM, Davidson JRT. A placebo-controlled study of Kava kava in generalized anxiety disorder. Int Clin Psychopharmacol. 2002;17(4):185-8. DOI: 10.1097/00004850-200207000-00005

2. Sarris J, Kavanagh DJ, Byrne G, Bone KM, Adams J, Deed G. The Kava Anxiety Depression Spectrum Study (KADSS): A randomized, placebo-controlled crossover trial using an aqueous extract of Piper methysticum. Psychopharmacology (Berl). 2009;205(3). DOI: 10.1007/s00213-009-1549-9

3. Sarris J, Stough C, Bousman CA, Wahid ZT, Murray G, Teschke R, et al. Kava in the treatment of generalized anxiety disorder: A double-blind, randomized, placebo-controlled study. J Clin Psychopharmacol. 2013;33(5). DOI: 10.1097/JCP.0b013e318291be67

5.2.6 Silexan or lavender extract

- **Question**

What is the comparative effectiveness and safety of silexan (lavender extract) compared with lorazepam and placebo in adults with GAD?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. Due to the limited and low-confidence evidence available, a recommendation cannot be made on the use of silexan (lavender extract) to improve symptoms in people with GAD.

- **Rationale**

The GUG has decided not to make a recommendation for or against the use of silexan in patients with GAD, taking into account the quality of the evidence and the benefit-risk balance.

Overall certainty of the evidence on effects: The overall quality of the evidence for both comparisons, from a single RCT with 395 participants, was rated low due to small sample size, imprecision of the effect and possible risk of bias, as there was insufficient information to assess the blinding of outcome assessors. The variables likehood of referral and level of concern were not reported in any of the studies.

Benefit-risk balance: no benefit is observed with silexan treatment compared to lorazepam; a small benefit is observed compared to placebo but there is no evidence on the expected undesirable effects, therefore, the benefit-risk balance is unknown.

- **Complete clinical question**

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- **References**

1. Kasper S, Gastpar M, Müller WE, Volz HP, Möller HJ, Schläfke S, et al. Lavender oil preparation Silexan is effective in generalized anxiety disorder - A randomized, double-blind comparison to placebo and paroxetine. Int J Neuropsychopharmacol. 2014;17(6). DOI: 10.1017/S1461145714000017

2. Woelk H, Schläfke S. A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. Phytomedicine. 2010;17(2). DOI: 10.1016/j.phymed.2009.10.006

5.2.7 Jiu Wei Zhen Xin herbal granules

- **Question**

In adults with GAD, what is the comparative effectiveness and safety of Jiu Wei Zhen Xin herbal granules compared to azapirones and SSRIs?

- **Recommendations**

EVIDENCE-BASED RECOMMENDATION

1. It is suggested that individuals diagnosed with GAD avoid consuming Jiu Wei Zhen Xin herbal granules as an alternative treatment to selective serotonin reuptake inhibitors or azapirones. [Weak recommendation against]

- **Rationale**

A weak recommendation has been made against the use of Jiu Wei Zhen Xin herbal granules in patients with GAD. The GUG has considered the magnitude of the expected effects, the quality of the evidence, the benefit-risk balance and the feasibility of implementing the recommendation.

Magnitude of the expected effects: the evidence indicates that treatment with Jiu Wei Zhen Xin herbal granules, both in comparison with treatment with azapirones and in comparison, with treatment with SSRIs, does not modify the levels of anxiety, the response rate or the levels of adverse events.

Overall certainty in the evidence on the effects: the overall quality of the evidence considered for the comparison of granules versus azapirones, from 8 RCTs with a total of 923 participants, is very low, while for the comparison of granules versus SSRIs, from 6 RCTs with a total of 435 participants, it is low. In the case of the first comparison, the judgement is due to the results presenting moderate heterogeneity, the effect being imprecise and there being a possible risk of bias given the insufficient information available to evaluate the domains of allocation concealment and incomplete outcome data. In the second comparison, the judgement on the certainty of the evidence is due to the small sample size and the risk of bias in the domains of allocation concealment and blinding of personnel and participants. The variables probability of remission and level of concern were not reported in any of the studies.

Benefit-risk balance: given that no benefit is observed in the treatment with Jiu Wei Zhen Xin herbal granules compared to azapirones and SSRIs and the expected undesirable

effects are not modified, the GUG has considered that the benefit-risk balance does not favour either the intervention nor the comparison.

Feasibility: Jiu Wei Zhen Xin herbal granules are not included in all the lists of medicines or dietary products in the programmes used in PC.

• Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

• References

1. Yang QZ, Yang H, Fan ZL, Huang XP, Zhou XY. Effective observation of Jiuweizhenxin Granula and Tandospirone in the treatment of generalized anxiety disorder. China Pharm. 2013;22:99-100.

2. Ji FF. Clinical study on the treatment of generalized anxiety disorder with combination of buspirone and Jiuweizhenxin Granula in the treatment of generalized anxiety disorder. China Pharm. 2015;1355-7.

3. Guo LC, Dong XG, Zeng DZ, Wang BH. Clinical observation on 50 cases of generalized anxiety disorder treated with Jiuwei Zhenxin Granula combining with Buspirone. Chin J Tradit Med Sci Technol. 2012;19:568-9.

4. Liu ZH. Control study of Jiuwei Zhenxin Granula and Buspirone in the treatment of generalized anxiety disorder. J Psychiatry. 2013;26:452-3.

5. Wang YJ, Chen DF, Wang CY. Efficacy and safety of Jiuwei Zhenxin Keli in treatment of generalized anxiety disorder: A multi-center randomized double-blind controlled trial. Chin Ment Health J. 2013;27(2). DOI: 10.3969/j.issn.1000-6729.2013.02.009

6. Pan YY, Wang YY, Liu Y. Effects of Jiuwei Zhenxin essence granules on oxidative stress in patients with generalized anxiety disorder. J Mod Integr Med. 2016;36:4044-6.

7. Zhang DF, Zeng DZ, Hu YL, Wang BH. Clinical observation on 40 cases of generalized anxiety disorder treated with Jiuwei Zhenxin Granula combining with Buspirone. Guid J Tradit ChineseMedicine Pharm. 2012;18:30-2.

8. Wu XF, Lan KR, Ji LY. Clinical observation on 30 cases of generalized anxiety disorder treated with Jiuwei Zhenxin Granula. China Pharm. 2012;21:106-7.

9. Wang S, Zhao LL, Qiu XJ, Wang DS, Tang T, Luo JK, et al. Efficacy and Safety of a Formulated Herbal Granula, Jiu Wei Zhen Xin, for Generalized Anxiety Disorder: A Meta-Analysis. Evid Based Complement Alternat Med. 2018;7(2018):9090181. DOI: 10.1155/2018/9090181

10. Ren L, Guo P, Gang S, al E. Clinical observation on 33 cases of generalized anxiety disorder treated with Jiuweizhenxin Granula. Med Her. 2015;1:64-6.

11. Zhang HG, Zhang XH, Cheng M, Wu WL, Wang CY. Clinical effect of Paroxetine and Jiuweizhenxin Granula in the treatment of generalized anxiety disorder. China J Mod Med. 2012;22:37-40.

12. Liang J. Clinical observation of Jiuweizhenxin Granula in the treatment of generalized anxiety disorder. J China Pharm. 2014;2078-9.

13. Liang J. Clinical observation of Jiuweizhenxin Granula in the treatment of generalized anxiety disorder. Chin J Pharmacoepidemiol. 2012;21:381-2.

14. Ren Y, Hu H. Clinical observation on 30 cases of female generalized anxiety disorder treated with Jiuweizhenxin Granula of cardiosplenic asthenia. Hunan J Tradit Chin Med. 2015;8:59-60.

5.2.8 Oriental herbal medicine

5.2.8.1 Oriental herbal medicine as a sole treatment

- ## Question

In adults with GAD, what is the comparative effectiveness and safety of oriental herbal medicine compared to anxiolytics and placebo?

- ## Recommendations

EVIDENCE-BASED RECOMMENDATION

1. Although the benefits of treatment with herbal medicine probably outweigh the harms, low confidence in the available evidence does not allow a recommendation in favour of herbal medicine for improving symptoms in people with GAD.

- ## Rationale

This clinical question analyses the scientific evidence and provides recommendations on the use of oriental herbal medicine as monotherapy in patients with GAD. The GUG has decided not to issue a recommendation for or against its use, taking into account the quality of the evidence and the feasibility of the treatment in our context.

Overall certainty in the evidence on the effects: The overall quality of the evidence was considered very low both for the comparison of oriental herbal medicine with placebo (4 RCTs, n=251) and for the comparison with anxiolytics (48 RCTs, n=4425), mainly due to the substantial unexplained heterogeneity of results between studies and the risk of bias due to the non-blinding of patients, personnel and outcome assessors. The studies considered only report the outcomes of anxiety level and risk of adverse events.

Feasibility: Oriental herbal medicine is not included in all the repertoires of medicines or diet therapy products of the programmes used in PC.

- ## Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- ## References

1. Park DM, Kim SH, Park YC, Kang WC, Lee SR, Jung IC. The comparative clinical study of efficacy of Gamisoyo-San (Jiaweixiaoyaosan) on generalized anxiety disorder according to differently manufactured preparations: Multicenter, randomized, double blind, placebo controlled trial. J Ethnopharmacol. 2014;158(PART A). DOI: 10.1016/j.jep.2014.10.024

2. Hou JC. Clinical Study on Treatment of Generalized Anxiety Disorder(syndrome of Liver Qi Depression or Hyperactive Heart Fire) with Ganlian Bu Ping Granule [PhD Thesis]. Changchun University of Traditional Chinese Medeicine; 2009.

3. Li QY. Particles in the Treatment of Generalized Anxiety Disorder (Yin Xun Yang Kang, Xin Shen Bu Ning Zheng) Clinical Study [PhD Thesis]. Hubei College of Traditional Chinese Medicine; 2009.

4. Feng GK, Chen YY, Li LJ, al E. Clinical research of Chailong jieyu pill in treating generalized anxiety disorder. J Nanjing Univ Tradit Chin Med. 2015;31(3):214-7. DOI: 10.14148/j.issn.1672-0482.2015.0214

5. Kwon CY, ji Choi E, weon Suh H, Chung SY, Kim JW. Oriental herbal medicine for generalized anxiety disorder: A systematic review of randomized controlled trials. Eur J Integr Med. 2018;20(April):36-62. DOI: 10.1016/j.eujim.2018.04.003

5.2.8.2 Oriental herbal medicine combined with anxiolytics

• Question

In adults with GAD, what is the comparative effectiveness and safety of oriental herbal medicine combined with anxiolytics, as opposed to anxiolytics alone?

• Recommendations

1. In people with GAD, the concomitant use of oriental herbal medicine and anxiolytics is not recommended. [Weak recommendation against]

• Rationale

A weak recommendation has been made against the concomitant use of oriental herbal medicine and anxiolytics. The GUG has considered the magnitude of the expected effects, the quality of the evidence and feasibility.

Magnitude of expected effects: according to the results, no benefit was observed from the concomitant use of oriental herbal medicine and anxiolytics compared to anxiolytics alone; nor were any undesirable effects observed.

Overall certainty of the evidence on the effects: the overall quality of the evidence considered is low despite coming from 33 RCTs with 2,415 participants. This is because the results show moderate to substantial heterogeneity that is not explained by subgroup analysis, and there is a risk of bias because it was not possible to blind patients, staff, or outcome assessors. The studies only report the outcomes of anxiety level and probability of adverse events.

Feasibility: Oriental herbal medicine is not included in all drug or diet therapy product repertoires of the programmes used in PC.

• Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-7

- ## References

1. Kwon CY, ji Choi E, weon Suh H, Chung SY, Kim JW. Oriental herbal medicine for generalized anxiety disorder: A systematic review of randomized controlled trials. Eur J Integr Med. 2018;20(April):36-62. DOI: 10.1016/j.eujim.2018.04.003

6. Referral to specialised mental health care

• Question

What are the criteria for referring patients with GAD to specialised mental health care?

• Recommendations

GOOD CLINICAL PRACTICE

1. It is recommended that patients with severe GAD and/or GAD with the following criteria be referred to the Mental Health Service:
   a. Psychiatric or organic comorbidity (major depression, alcohol dependence and/or substance abuse)
   b. Suicidal ideation (urgent referral)
   c. Persistent high anxiety after more than 12 weeks of pharmacological treatment and/or psychotherapy
   d. Very disabling symptoms (social and occupational adaptation)

2. In patients with GAD who do not respond to cognitive behavioural therapy, or in second line to relaxation therapy, metacognitive therapy or acceptance and commitment therapy, and in whom two antidepressant treatment options have been tried without response (12 weeks of treatment at an adequate dose), referral to a specialist in psychiatry is recommended for a second opinion on the diagnostic validity, the treatment plan, adherence to it and the usefulness of other therapeutic options.

In the event of uncertainty regarding the suitability of the treatment, the dosage, or the follow-up, it is suggested to consider the option of an integrated or virtual consultation with specialised Mental Health care, if available.

• Rationale

The GUG has decided to formulate a series of general practical considerations because it understands that it is not possible to recommend specific interventions based on the evidence found, which is scarce and of very low-quality. The GAG has taken into account the recommendations of current CPGs of high methodological quality on TAG, in addition to its own clinical experience.

These recommendations are aimed at the assessment of patients with severe comorbidity, as they require more complex treatments and closer follow-up by specialists in the field.

It is also important to bear in mind that in patients who do not improve after the various proposed interventions, the diagnostic validity or accuracy of the treatment should be reassessed, as they may require other, more complex therapeutic options.

Finally, the GAG considers fluid communication between professionals at different levels to be good practice in order to streamline consultations and reduce waiting times, all with the aim of providing the patient with the best possible care.

- ## Complete clinical question

Complete information on this question (available in Spanish):

https://portal.guiasalud.es/guia-en-capas/gpc_641_trastorno_ansiedad_generalizada_ap/#question-8

- ## References

1. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113] [Internet]. NICE; 2011. Disponible en: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997

2. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12):1109-72. DOI: 10.1177/0004867418799453 DOI: 0004-8674