**Final GAD RECOMMENDATIONS & EVIDENCE**

# Recommendation 1: Diagnosis of Generalized Anxiety Disorder (III-2)

It is recommended for general practitioners and other Primary Health Care doctors to consider the diagnosis of Generalized Anxiety Disorder for people who visit PHC frequently and need reassurance about chronic physical health problems and present symptoms of ongoing anxiety and are repeatedly worrying about a wide range of different issues.

**Level of Evidence: III-2**

**Evidence Statement**

NICE [1] Guidelines and recent observational studies[2,3,4], report that patients with GAD in primary care complain of physical symptoms more often than psychological or repeating worry. Patients with GAD mostly consult primary care for aches, sleep problems and somatic problems. Somatic complaints of patients usually appear in the form of chronic medical conditions such as chest pain, chronic fatigue syndrome, irritable bowel syndrome and hypertension, diabetes and cardiac diseases. The diagnosis of GAD is possible to these patients who are frequently visiting primary care having the symptoms above.

# Recommendation 2: Screening questionnaires for GAD in Primary Care (III-2)

It is recommended for general practitioners and other Health Care Professionals in PHC to consider before screening, the use of specific questions:

- Do you worry excessively about everyday things such as your family, your health, work or finances? Does your family or your loved ones tell you that you worry too much?
- Do you have difficulty in controlling your worry and does this interferes with your work, your activities, your relationships or your physical health?

**Level of Evidence: III-2**

**Evidence Statement**

Spanish Guidelines[5] suggest the use of specific interview questions during medical history taking. These questions help primary care doctors for detection of GAD. These questions, whose source is Canadian Guidelines[6], are useful, especially in countries like Greece, where GAD-2 and GAD-7 are not officially validated.

## Recommendation 3: Screening questionnaires for GAD in Primary Care (III-2)

If you suspect GAD it is recommended for general practitioners and other PHC doctors the use of GAD-2 (Generalized Anxiety Disorder-2) or GAD-7 (Generalized Anxiety Disorder-7) diagnostic questionnaires.

**Level of Evidence: III-2**

**Evidence Statement**

In primary care GAD-2 and GAD-7 scales have high sensitivity and specificity for detecting GAD. They are brief, easily to use and the most common GAD screening tools in PHC.[7,8] On the contrary, similar questionnaires like PHQ-9 and HADS are longer and pose difficulties for translation and cross-cultural use.[9,10]

## Recommendation 4: Psychological therapies (I)

It is recommended for general practitioners and other PHC professionals, to initiate, after appropriate training, the use of Cognitive Behavioral Therapy and Applied Relaxation or/and in initiating simultaneously with pharmacological treatment or to refer to a specialist or Mental Health Services.

**Level of Evidence: I**

**Evidence Statement**

According to NICE Guidelines[1] that rely on 21 RCT's and other, recent RCT's[11,12] is supported that cognitive behavioural therapy (CBT) is the most effective psychological intervention for GAD in primary health care. In these studies, CBT was compared mainly with applied relaxation and psychodynamic psychotherapy. Response to treatment and remission of GAD's symptoms (mainly anxiety) are immediately observed and tend to remain after 6 and 12 months follow-up.

According to recent meta-analysis and reviews[13,14,15,16,17.], CBT is effective in treating anxiety, both in the short term, as well as over time. Analysis also revealed that CBT is effective in maintaining treatment gains for up to a year.

## Recommendation 5: Other Psychological Therapies and Life-style (I)

Other psychological interventions like guided self-help, non facilitated self-help and psycho-educational groups should be provided on an ongoing basis by appropriate trained general practitioners and other health care professionals before drug therapy or simultaneously to it.

**Level of Evidence: I**

**Evidence Statement**

According to NICE Guidelines[1] and 2 recent meta-analysis,[18,19] other psychological therapies, like guided self-help, non facilitated self-help and psychoeducation have been proven effective in primary care for patients diagnosed with GAD, mainly for anxietysymptoms and the absence of comorbidity.

## Recommendation 6: Other Psychological Therapies and Life-style (I)

It is recommended for general practitioners and other PHC professionals to suggest smoking cessation, regular exercise and in general healthy lifestyle to all patients with GAD for the reduction of anxiety symptoms.

**Level of Evidence: II**

**Evidence Statement**

A systematic review and meta-analysis of 26 observational studies[20], measured anxiety, depression, mixed anxiety and depression, psychological quality of life, positive affect, and stress in quitters

compared with continuing smokers. Smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life.

Physical exercise can be significantly helpful for patients with GAD. According to 1 RCT[21] physical exercise is an attainable, low-risk treatment that proved to be effective in the reduction of GAD's anxiety symptoms and can be used as a long-term therapy. One systematic review[22] investigated the therapeutical outcome of physical exercise-aerobic and non aerobic- for anxiety disorders. Results showed that physical exercise is effective in reducing anxiety symptoms. However, more well-designed studies are needed, that specify the type and frequency of exercise that shows effectiveness.

## Recommendation 7: Other Psychological Therapies

It is recommended for general practitioners and other PHC doctors to suggest to patients with GAD and with essential web skills, a guided i-CBT, a relatively new therapeutical intervention with significant results so far, regarding GAD. Accreditaly i-CBT programs could be recommended to patients and should be provided by appropriately trained healthcare professionals.

**Level of Evidence: I**

**Evidence Statement**

Guided CBT through Internet is a relatively new therapeutic approach for people suffering from GAD and is an efficacious and wide acceptable treatment especially by young people with therapeutic gain remaining for 1-3 years. It is a practical, alternative approach, especially for those that otherwise would remain without treatment. These results are sustained by 1 meta-analysis[23] and recent RCT's[24,25,26].

## Recommendation 8: First-line Drug Therapy (I)

It is recommended for general practitioners and other PHC doctors to initiate the pharmacological treatment with one antidepressant of SSRI's or SNRI's.

**Level of Evidence: I**

**Evidence Statement**

According to 2 recent systematic reviews[27,28] SSRI's and SNRI's are the most effective pharmaceutical therapy for GAD. Namely, the most effective drugs for the treatment of GAD are: Sertraline, escitalopram, paroxetine, duloxetine and venlafaxine. Comparison of the above drugs did not clearly indicate significant clinical difference regarding dose-dependent response to treatment.

IPAP[29] algorithm and NICE[1] suggest that a SSRI or a SNRI should be the initial treatment for GAD. In case of unsatisfactory response to treatment with adequate dosing, another drug from the same category (SSRIs/SNRIs) should be used.

## Recommendation 9: Benzodiazepines (I)

It is recommended for general practitioners and other PHC doctors in case of deciding to prescribe benzodiazepines, in combination with SSRI's to prescribe them no longer than 2 weeks for the treatment of GAD symptoms or while waiting for response to antidepressants.

**Level of Evidence: I**

**Evidence Statement**

12 RCTs support NICE[1] recommendations, found benzodiazepines to be effective drugs during the acute phase of GAD. Newer reviews also confirm the effectiveness and the rapid action of benzodiazepines in patients with GAD.[30,31] Baldwin D. (2005)[32] suggests a short-term treatment up to 4 weeks, in order to avoid the risk of addiction and adverse effects. It has been observed that the use of benzodiazepines in elderly patients increase the possibility of falls and fractures, especially of the hip, confusion and cognitive reduction. In order to avoid benzodiazepines' adverse effects, general practitioners should prescribe the lowest adequate doses and not longer than 2-4 weeks, especially when the aim is immediate control of symptoms, while waiting response to treatment with antidepressants[1, , 30, 31, 32, 33,34].

A Meta-Analysis by Mugunthan[35] et al. (2011) reports that general doctors' short intervention in patients with long-term benzodiazepines' intake was found to be effective in reducing or ceasing the medication, without inducing adverse effects.

## Recommendation 10: Other Pharmaceutical Options (I)

In case of non-response to drug treatment it is recommended to general practitioners and other PHC doctors the use of pregabaline or venlafaxin or azapirones or tricyclic antidepressants.

**Level of Evidence: I**

**Evidence Statement**

According to NICE Guidelines[1], in case of non-response to first-line treatment, pregabaline is an efficacious therapy for GAD and exerts a greater effect against anxiety symptoms, compared with somatic anxiety symptoms. Duloxetine, azapirones, buproprion, benzodiazepines and imipramine have also demonstrated effectiveness for GAD. These conclusions are verified by other recent studies[25,28,29].

In a meta-analytic review[30] azapirones appear to be useful for GAD treatment, especially for the patients that have not taken benzodiazepines before. According to a recent review[36] azapirones may not be superior to benzodiazepines and not as acceptable as benzodiazepines. Their adverse effects seem to be mild, not severe, and include physical symptoms such as nausea and dizziness[1,30,36] It can't be concluded whether azapirones are more effective than benzodiazepines, anti-depressants, psychotherapy, hydroxyzine or kava-kava, for this more studies are needed in order to prove their effectiveness.

Buspiron is rarely used as mono-therapy for GAD. More often, is used as a complementary drug together with first-line treatment due to late onset of its action and absence of benefit in case of comorbidity with other diseases, especially depression[33,37].

## Recommendation 11: Atypical antipsychotics (II)

The prescription of atypical antipsychotics is suggested to be utilized with caution by general practitioners and other PHC doctors, after consulting a specialist or a member of mentalhealth team.

**Level of Evidence: II**

**Evidence Statement**

In the past, some typical antipsychotics have been approved for anxiety disorders and recent studies suggest that atypical antipsychotics may have role in GAD's treatment. The majority of the

studies compare quatiepine versus placebo in order to test its efficacy as monotherapy in GAD using doses 50-150 mg/day[40,41], but still quetiapine cannot be recommended as a routine-therapy. More studies are needed regarding its safety and efficacy in primary health care, mainly because of the danger of metabolic syndrome and the adverse effects that include mouth-dryness, dizziness, insomnia, fatigue and headaches. Nevertheless, the use of quatiepine could be considered in the future for the treatment of GAD, if other drug categories will be proven ineffective or when certain symptoms are present.

According to a recent open-label trial of risperidone,[42] 30 patients with a primary diagnosis of an anxiety disorder including GAD, received antidepressants and/or benzodiazepines of at least 8 weeks augmented with risperidone. Although conclusions are limited by the open-label, data suggest that augmentation with low-dose risperidone may be a useful option for patients with anxiety disorders.

According to a recent double-blind RCT[43], olanzapine, risperidone and quetiapine immediate release have been explored in the treatment for refractory GAD and risperidone in bipolar anxiety, but the results were not consistent. By contrast quetiapine XR 150 mg/day monotherapy yielded consistent anxiolytic effects. In a 52-week treatment of GAD, quetiapine XR was superior to placebo in the prevention of anxiety relapses.

Overall atypical antipsychotics were relatively well tolerated with common side effects like somnolence. However in contrast to antidepressants and benzodiazepines the long-term risk and benefit of atypical antipsychotics in the treatment of GAD is yet to be determined.

## Recommendation 12: Comorbidity (III-2)

It is recommended to general practitioners and other PHC professionals, while diagnosing, prescribing and managing non responders to therapy, to consider comorbidity of GAD with other mental disorders and physical health problems.

**Level of Evidence: III-2**

**Evidence Statement**

GAD is a disease that is often comorbid with other mental disorders such as emotional (mainly depression) and other anxiety or somatoform disorders, unexplained medical symptoms, substance abuse, alcohol misuse and other psychiatric diseases. GAD is also related with physical diseases such as heart, gastrointestinal, lung (like asthma) and thyroid-gland diseases, arthritis and other disorders with chronic physical pain, as it is supported by recent observational studies[44,45], NICE Guidelines[1] and Spanish Guidelines[5].

## Recommendation 13: Treatment of Comorbidity (III-2)

It is recommended for general practitioners and other PHC doctors, for patients with GAD and other mental health disorders, to initiate treatment from the most severe one, which affects the functionality of patients. In case of GAD comorbidity with physical diseases, it is recommended the simultaneously therapeutic management.

**Level of Evidence: III-2**

**Evidence Statement**

Given the fact that GAD is highly comorbid with depression and other anxiety disorders, a question aroused is, which disorder should be treated first. Older NICE Guidelines[46] (2004) suggest that depression should be treated first, whilst those published in 2009[47] argue that anxiety should be treated initially, taking into account that reduced anxiety improves depression. In case of comorbid alcohol misuse, alcohol misuse should be treated first because it might lead to a significant reduction of GAD symptoms, according to the most recent NICE Guidelines[1] (2011).

Generally, basic aim is to treat the most severe disorder first so that the patient achieves higher functionality levels.

## Recommendation 14: Follow-up of GAD comorbidity (III-2)

It is recommended for general practitioners and other PHC doctors, to provide into an ongoing basis, assessment of comorbidity with depression, substance abuse or physical illness.

**Level of Evidence: III-2**

**Evidence Statement**

According NICE Guidelines[1], supported by epidemiological studies[48,49,50,51,52,53,54,55], as part of the total assessment for GAD and given the fact that comorbidity affects the development and the severity of the disease, comorbidity with depression, substance abuse, personality disorders and physical illness is recommended to be taken into account, especially for patients with poor or none response to treatment.

## Recommendation 15: Prevention in general population (II)

It is recommended for general practitioners and other PHC doctors, to encourage general population on lifestyle activities in order to reduce risk for developing GAD.

**Level of Evidence: II**

**Evidence Statement**

Mrazek and Haggerty[56] suggest 3 types of the above interventions for the prevention of mental disorders. From the 3 types of preventive interventions, the suggested prevention resembles the conventional treatment and has the best probability to detect groups of people with subthreshold condition who have a greater risk in developing major depression and anxiety disorders. Indicated prevention aims also to reduce severity of symptoms and time spent in the subthreshold condition[57,58,59,60, 61, 62].

A recent RCT[63] evaluated the efficacy of a preventive program for depression and anxiety disorders in 170 elderly patients (≥75 years old) with subthreshold symptoms who did not fully meet the criteria for the diagnosis of depression or an anxiety disorder. Stepped-care preventive program was found capable of reducing the risk of depression and anxiety disorders, but it has been tested only in the elderly therefore the outcomes can't be generalized. Nevertheless, constitutes a useful program to be further researched.

## Recommendation 16: Prevention in high-risk groups (II)

It is recommended general practitioners and other PHC doctors, to detect people with high risk for GAD and to undertake specific actions.

**Level of Evidence: II**

**Evidence Statement**

Mrazek and Haggerty[56] suggest 3 types of the above interventions for the prevention of mental disorders. From the 3 types of preventive interventions, the suggested prevention resembles the conventional treatment and has the best probability to detect groups of people with subthreshold condition who have a greater risk in developing major depression and anxiety disorders. Indicated

prevention aims also to reduce severity of symptoms and time spent in the subthreshold condition[57,58,59,60, 61, 62].

## Recommendation 17: Referral (III-2)

It is recommended for general practitioners and other PHC doctors, referral to a Mental Health Specialist, if the patient with GAD has severe anxiety and functional impairment in conjunction with a risk of self-harm or suicide or significant comorbidity or self-neglect or an inadequate response to previous psychological and drug interventions.

**Level of Evidence: III-2**

**Evidence Statement**

According to NICE[1] patient's referral to Mental Health Services should be considered when patient suffers from severe anxiety and significant functional reduction combined with: Self-injury/suicide danger or significant comorbidity (such as substance misuse, personality disorders or complicated physical health issues) or self-neglect or insufficient response to 3rd stage therapeutical interventions of the Stepped Care Model.

According to Spanish Guidelines[5] the referral criterions are: Difficulty/uncertainty in diagnosis or mental/physical comorbidity (such as major depression, alcohol dependence and/or substance/drug use) or suicidal ideation (urgent referral) or persistent and severe anxiety for more than 12 weeks of pharmaceutical and/or psychotherapeutic support or significant symptoms that lead to disability (social and/or work adjustment).

## Recommendation 18: Role of nurse and other PHC Professionals (III-2)

It is recommended the trained PHC nurse and other Health Care Professionals in GAD, to have an active role, in detection, monitoring, treatment information and evaluation of the disease, in education of the patient about the nature of GAD, in providing information about therapeutic options, their implementation and patients follow-up.

**Level of Evidence: III-2**

**Evidence Statement**

Studies focused in nursing interventions are limited in patients with anxiety disorders. According to 1 recent observational study[64] (qualitative), mental-health nursing interventions (30 participants) for patients experiencing anxiety were investigated and described in 2 mental health departments. Results acknowledge the significance of nursing contribution in detection, evaluation of the disease, in developing a therapeutic relationship with the patient and showing empathy, in patients' education about the nature of the disease, in providing information about therapeutic options and patient's follow-up.

Similar to previous conclusions are also the instructions of Nursing Royal College of U.K. cited in a handbook[65] developed for specially trained primary health care nurses in mental health issues.

## Recommendation 19: Health Care Professional's Education for GAD (III-2)

It is recommended for general practitioners, other PHC doctors and Health Care Professionals to be trained in detection and evaluation of GAD, in counselling and psychotherapeutical support and empathy, which leads to a better follow-up and management of the disease.

**Level of Evidence: III-2**

**Evidence Statement**

According to a NICE guidelines' study[66] and recent observational studies[67,68,69,70] it was found that there are difficulties in detection, diagnosis and management of anxiety and depression from general practitioners.

According to an educational package for healthcare professionals about the diagnosis and management of anxiety disorders in primary care in Canada[71], the recommended skills of healthcare professionals in primary care for the better management of GAD is the detection of GAD, differential diagnosis from other anxiety or mental disorders and the ability to construct a therapeutic relationship through empowering, acceptability, confidence and disposal of collaboration with the patient. All these sectors are described in various observational studies with regard to the abilities of healthcare professionals in primary care for the management of GAD[72,73,74].

According to a recent RCT[75] the effectiveness of an education programme for interviewing skills in managing patients with depression and anxiety among Chinese general practitioners was assessed. The results revealed that only certain communication skills, such as active listening and facilitating patient's response can be taught in the management of depression and GAD in Chinese primary care physicians.

Various observational studies from Greek and International literature[76,77,78,79,80] notice that knowledge and attitudes of general practitioners in the detection, pharmaceutical and psychological

therapy of anxiety disorders can influence their clinical practice. Effective educational interventions and recommendations should be designed and implemented for healthcare professionals in primary care on these fields.

A report[81] «Integrating mental health into primary care», by WHO and WONCA, mentions that a primary care training in mental health is more effective, when: it clearly meets local needs, it is clearly relevant to primary care, it is focused in those who need it, it is adopted by the target audience (healthcare professionals, patients), it is linked to the existing mental health system (education about referral and back-referral framework) and supported by ongoing follow-up[82].

## Recommendation 20: Use of Health Services for Special Population Groups (III-2)

It is recommended to general practitioners and other PHC professionals to pay specific attention for special population groups (immigrants, Roma, elderly people, inhabitants in remoted areas) to facilitate their access to health services, taking into consideration their cultural differences and educational level.

**Level of Evidence: III-2**

**Evidence Statement**

According to recent observational studies, there is a lower use of mental health services among elderly[83] and ethnic minorities[84]. There are differences in clinical presentation of GAD, mainly with physical symptoms[85] and greater possibility for these patients not receiving their medication[86]. Our therapeutic choices should match with their culture[87] and should be effective in these groups, according to 1 recent RCT[88] (e.g. i-CBT).

## Recommendation 21: Patients records (III-2)

GPs and other PHC physicians should keep patient record for patients with GAD in order to monitor their care.

**Level of Evidence: III-2**

**Evidence Statement**

According to a recent cross-sectional study[89] general practitioners recognized anxiety disorders better than previously when all medical record data were taken into account.

## Recommendation 22: Home Health Care (IV)

It is recommended to GPs and other Health Care Professionals PHC physicians to cooperate with services and programs of domically care.

**Level of Evidence: IV**

**Evidence Statement**

A brief[90] highlights the integration of physical and mental health care as an important aspect of the Medicaid health home model. Collaborative care programs are one approach to integration in which primary care providers, care managers, and psychiatric consultants work together to provide care and monitor patients' progress. These programs have been shown to be for a variety of mental health conditions.

## Recommendation 23: Health care services and Technology (I)

It is recommended the GPs and other PHC physicians as well as PHC professionals to use telemedicine and other technologies in order to improve the quality of life of patients with Generalized Anxiety Disorder.

**Level of Evidence: I**

**Evidence Statement**

A recent review[91] aimed to determine the clinical effectiveness of remotely communicated, therapist delivered psychotherapy. Thirteen studies were identified, ten assessing psychotherapy by telephone, two by internet and one by videoconference. The results revealed that telephone-based interventions are a particularly popular research focus and as a means of therapeutic communication may confer specific advantages in terms of their widespread availability and ease of operation.

A recent systematic review of reviews[92] reports on the evidence of the effectiveness of telemedicine with particular reference to both outcomes and methodologies for evaluation. 21 reviews concluded that telemedicine is effective, 18 found that evidence is promising but incomplete. Reviewers point to a continuing need for larger studies.

## Recommendation 24: Health care services and non-governmental organizations (III-1)

It is recommended to GP's and other PHC physicians as well as other PHC professionals to encourage patients with Generalized Anxiety Disorder to participate in programs and actions of associations or organizations in order to be motivated and improve their quality of life.

**Level of Evidence: III-1**

**Evidence Statement**

An open trial[93] reports the acceptability, feasibility and preliminary efficacy of an established iCBT treatment course administered by a not-for-profit non-governmental organization, to consumers with symptoms of anxiety. The present study points to the possibility that, with appropriate training and supervision, these organizations may have the capacity to provide internet-based psychological interventions and improve access to evidence-based treatments. However, much more research is needed.

# Practical algorithm