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MOH Protocols for the Management of Anxiety Disorders

Generalized Anxiety Disorder, Social Anxiety Disorder and Panic Disorder

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- **Introduction**

Anxiety and related disorders are some of the most common mental disorders, having lifetime prevalence rates of up to 31% (1–5) and 12-month prevalence rates of about 18%. (3, 4). Individual disorders have a wide range of rates. Compared to men, women have greater prevalence rates for most anxiety disorders (4, 5, 6). In a national survey in Saudi Arabia, panic disorder was found to be prevalent by 1.6 %, generalized anxiety disorder was found to have a prevalence rate of 1.9 %, and social anxiety disorder was found to be prevalent by 5.6 % (7).

Anxiety and associated disorders place a substantial financial and emotional strain on patients and their families (8). In addition, they're linked to significant functional impairment, which gets worse as anxiety gets worse (9) or as the number of comorbid anxiety disorders grows (10, 11). Furthermore, research has shown that patients with various anxiety and associated disorders have a lower quality of life (12, 13). Anxiety also has a significant economic effect on society, as it is linked to increased use of healthcare services (5, 14) and worse productivity at work (14, 15).

A. Purpose

Anxiety and related disorders are prevalent in clinical practice, and they are commonly associated with other psychiatric and medical conditions. A thorough grasp of pharmacological and psychological treatments' efficacy and side effect profiles is required for optimal management. There is a clear need to create a MOH protocol for the Management of Anxiety disorder due to highly variable practice. As a result of an initiative of the Ministry of Health of the Kingdom of Saudi Arabia, a group of expert psychiatrists reviewed multiple published protocols of Management of Anxiety Disorder that aims to facilitate standardized care so that all patients with anxiety disorders receive optimal treatment that is evidence-based and creates adapted protocols for the health care provider.

B. Aim & scope

These protocols aim to deliver evidence-based recommendations on the non-pharmacological and pharmacological management of some common anxiety

disorders, specifically Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder for adult patients. Other anxiety disorders, for example, Simple phobic disorder, secondary anxiety disorder, and other anxiety disorders mentioned in DSM-5 and ICD-11 were not addressed in this protocol. Also, this protocol doesn't cover specific populations such as anxiety in children, the elderly, pregnant women, or patients with comorbid other medical conditions. This protocol also aims to reduce unnecessary use of some psychotropics like antipsychotic and benzodiazepine in Anxiety Disorder and to ensure that, were unavoidable, they are prescribed according to best practice.

C. Targets

The protocol is intended to be a practical protocol and ready reference for health professionals who work in settings where they will be caring for patients with Anxiety Disorder. Given the extensive range of expertise, disciplines, and positions of employees at the MOH, it's impossible to capture the whole scope of specialist practice that can be used by experienced professionals across different disciplines and settings. As a result, this protocol can be applied in several cases. It provides an overview of fundamental principles and practical resources for less experienced employees, which they may implement and discuss with their supervisors. Multidisciplinary teams can utilize it as a shared reference point to aid in coordinated treatment, and more experienced professionals can use it as a refresher or training resource. The protocol should be applied within a framework of local policies and procedures.

D. Setting

- Iradah Complex / Hospital and Mental Health.
- Psychiatric clinics in MOH General Hospitals.

E. End Users

Psychiatry Consultants, Specialists and Residents, primary care physicians, Psychiatry clinical pharmacists, Pharmacists, Nurses.

Primary Care Physicians Role:

1- initially, primary care physician assesses the case for mental health disorders, if he provisionally diagnoses the case with Mild Generalized Anxiety Disorder, Social Anxiety Disorder and Panic Disorder he should manage the case in primary care setting.
2- Second, if the primary care assesses the case for mental health disorders and diagnoses the case with moderate to severe Generalized Anxiety Disorder, Social Anxiety Disorder and Panic Disorder he should refer the case to specialized psychiatry clinic.

2- After the case with moderate to severe Generalized Anxiety Disorder, Social Anxiety Disorder and Panic Disorder has been stabilized, and proper care was provided by the treating psychiatrist, who can refer back the case to primary care physician for regular follow up and continuing the psychiatric Management plan.

3- During follow up of a Known case with moderate to severe Generalized Anxiety Disorder, Social Anxiety Disorder or Panic Disorder in the primary care clinic, once the case showed any signs or symptoms of disorder relapse or any safety issues (e.g. suicidality or homicidally), primary care physician should refer the case to specialized psychiatry clinic for stabilization and management.

F. Methodology

This is the first version of the Saudi practical protocol on the management of Anxiety Disorder. This protocol development is completed through 2 phases:

Phase 1: literature review, and the MOH formulary adaptation along with reviewing multiple published protocols by a teamwork of a group of psychiatric consultants. The published protocols were evaluated using the Appraisal of Protocols, Research and Evaluation II (AGREE II) scale. A total of 4 protocols were reviewed including The Maudsley Prescribing Protocols in Psychiatry, 13th Edition (16) and UK National Institute for Health and Care Excellence (NICE) protocol, Generalized anxiety disorder and panic disorder in adults: management review 2019 (17), Psychopharmacology Algorithms Clinical

Guidance from the Psychopharmacology Algorithm Project at the Harvard (18), Canadian clinical practice protocols for the management of anxiety 2014 (19), and Royal Australian and New Zealand College of Psychiatrists clinical practice protocols for the treatment of social anxiety disorder, generalized anxiety disorder and panic disorder (20) meet the criteria for use in the development this protocol.

Phase 2: The protocol was sent to a group of experts in adult psychiatry to put their input and provide their review. Their input was collected over 3 weeks, followed by further meetings and assessment for the feedback by the committee.

G. Updating

The first version of this protocol was created in 2021. The protocol will be updated every three years or if any changes or updates are released by international/national protocols, pharmacotherapy references, or MOH formulary.

H. Conflict of interest

This protocol was developed based on valid scientific evidence. No financial relationships with pharmaceutical, medical device, and biotechnology companies.

I. Funding

No fund was provided.

J. DISCLAIMER

This Clinical protocol is an evidence-based decision-making tool for managing health conditions. It is based on the best information that is available at the time of writing, and is to be updated regularly. This protocol is not intended to be followed as a rigid treatment protocol. It is also not meant to replace clinical judgment of practicing physicians but is the only tool to help manage patients with anxiety disorder. Treatment decisions must always be made on an individual basis, and prescribing physicians must customize care and tailor treatment regimens to patients' unique situations and health histories. For dosage, special warnings and precautions for usage, contraindications, and monitoring of side effects and potential risks, physicians should check the approved product monographs within their institution's formulary. When choosing treatment options, take into account any constraints imposed by the institution's formulary. During the decision-making process for picking specific drugs within a recommended specialized class, prescribing physicians should consult their institution's formularies.

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• Protocol Overview (Summary)

- Determine Assessment and diagnosis of (generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder).
- Considering anxiety disorder as a result of a medical condition (e.g., hyperthyroidism) or a drug (e.g., caffeine), as well as comorbidity with other psychiatric illnesses (e.g., substance use disorder).

Initial treatment is determined by a variety of criteria, including the severity of the condition:

- Mild to Moderate:

CBT or Medication or CBT plus Medication.

- Severe:

CBT plus Medication.

- Examine the patient's response to the 1ST LINE therapy.
- After 4–6 weeks, assess progress.
- Treatment should last at least one year to be effective.

If there is a partial response or no response:

- ✓ Examine commitment and treatment involvement.
- ✓ Examine therapy goals and expectations, and rule out medication-related effects.
- ✓ Ensure that the treatment given was in accordance with the protocol.
- ✓ Re-evaluate comorbidity (depression, substance abuse).

Consider to continue, modify or augment the management plan based of the following treatment line of options:

1st line treatment options:

- **CBT alone or CBT with medication should be considered as first-line treatment.**
- **Selective Serotonin Reuptake Inhibitor (SSRI) e.g. :**
  - Fluoxetine 20-80 mg/day .
  - Escitalopram 10-20mg/day.
- **Serotonin and norepinephrine reuptake inhibitors (SNRIs) e.g.:**
  - venlafaxine 75-225mg/day.
  - Duloxetine 60-120 mg/day.

2nd line treatment options:

- **Tricyclic antidepressants e.g.:**
  - Imipramine 75-300 mg/day.
  - Amitriptyline 100-300mg/day.
- **Beta-Blocker e.g.** propranolol 40mg po q 8-12 hours.
- **Mirtazapine** 15-45mg/day.

3rd line treatment options:

- **In case of genitalized anxiety disorder**:
  - Valproic acid 500-2250 mg /day.*
  - Quetiapine 50-300 mg /day.*
  - Risperidone 0.5-1.5 mg / day.*

* All of these medication are supported by studies but Not FDA approved ((off-label))

Consider Benzodiazepines for short-term use only in the event of a crisis intervention owing to extreme anxiety symptoms; it is used for 2–4 weeks at most, especially for people who suffer from severe anxiety.

- **General Principles in Assessment and Management of Anxiety Disorder**

A. Assessment:

- ✓ Those who fulfil the diagnostic criteria for any of the anxiety disorders (generalized anxiety disorder, panic disorder, agoraphobia, and social anxiety disorder) using DSM-5 or ICD-11 diagnostic criteria, taking into consideration that anxiety disorders have similar causes and management, so protocols for one disorder will be similar to protocols for related disorders. (20)
- ✓ Considering anxiety disorder as a result of a medical condition (e.g., hyperthyroidism) or a drug (e.g., caffeine), as well as comorbidity with other psychiatric illnesses. (16)
- ✓ Consider GAD as a differential diagnosis in persons who have anxiety or a lot of worries, and those who go to the doctor a lot who: (16)
  1- Suffer from a long-term physical health issue.
  2- Are seeking comfort about somatic symptoms but do not suffer from a physical health issue (especially the elderly and people from minority ethnic groups).
  3- Are preoccupied with a variety of topics on a regular basis.
- ✓ The following are the main components of anxiety assessment: (19)
  1- Screen for the anxiety and related symptoms.
  2- Perform a differential diagnosis (consider severity, impairment, and comorbidity).
  3- Determine whether the patient has specific anxiety or associated disorder.
  4- Psychological and/or pharmacological treatment.
  5- Carry out follow-up.
- ✓ GAD-7 (21), Beck Anxiety Inventory (BAI) (22), Depression Anxiety Stress Scale (DASS), Social phobia scale and Panic disorder severity scale (23) are some of the scales that can be used to assist with screening and severity measurement.

B. Management:

The degree of the symptoms, patient preference and motivation, ability of the patient to be involved in treatment, availability of medications or psychotherapy services, initial reaction to treatment, side effect profile, and the existence of comorbid medical or psychiatric disorders are all factors to consider when choosing a pharmacological or non-pharmacological management model. (19)

All patients should be educated on their disorder, the efficacy (including the expected time for therapeutic effects to appear) and tolerability of treatment options, aggravating factors, and relapse symptoms. (19)

- **Combined Psychological and Pharmacological Treatment (First-line Treatment):**

During the acute treatment period and while medication was continued, a meta-analysis of 21 trials indicated that combining psychotherapy with antidepressant medications was greater than Cognitive Behavior Therapy (CBT) or pharmacotherapy alone [24, 25]. In addition, combined therapy was more effective than pharmacotherapy alone after treatment ended, and it was as effective as psychotherapy [24, 25]. Similar findings have been found in previous meta-analyses [26, 27, 28], implying that CBT alone or in combination with pharmacotherapy should be recommended as a first-line treatment.

Non-Pharmacological Management:

Several studies showed the efficacy of CBT in treating anxiety disorder (6), especially in panic disorder. A meta-analysis showed CBT techniques are favored over medication and had the most consistent evidence of efficacy for treating panic disorder. In addition, minimal intervention formats, such as self-help books (36-38), treatment via telephone/videoconferencing (36), and internet-based CBT (ICBT) (36) have been shown to be more effective than wait-list or relaxation controls.

Non-pharmacological treatment includes the following:

- ✓ Psychotherapy, mainly cognitive-behavioral therapy (CBT).
- ✓ Individual non-facilitated self-help

- ✓ Individual guided self-help
- ✓ Psychoeducational groups.

Components of cognitive-behavioral interventions (Boschen MJ, Oei TP: A cognitive-behavioral case formulation framework for treatment planning in anxiety disorders. Depress Anxiety. 2008, 25: 811-823.)

Exposure	• Encourage patients to confront their fears, as patients gain corrective information by experience. • Fear is extinguished via regular exposure. • Successful coping improves self-efficacy.
Safety response inhibition	• Patients restrict their regular anxiety-relieving behaviors (e.g., escape, need for reassurance). • Reduces negative reinforcement. • Coping with anxiety without using anxiety-relieving behaviors improves self-efficacy.
Cognitive strategies	• Cognitive restructuring, behavioral experiments, and related strategies target patients' exaggerated perception of danger (e.g., fear of negative evaluation in SAD). • Presents corrective information regarding the level of threat. • Can also target self-efficacy beliefs.
Arousal management	• Relaxation and breathing control techniques can help patients control increased anxiety levels.
Surrender of safety signals	• Patient foregoes safety signals (e.g., presence of a companion, knowledge of the location of the nearest toilet). • Patients learn adaptive self-efficacy beliefs.

Pharmacological management:

1- First-line drug therapy includes (2)

A- Selective serotonin reuptake inhibitor (SSRI)

B- Serotonin-norepinephrine reuptake Inhibitor (SNRI)

To treat depression, start with half the normal starting dose and gradually increase the dose into the normal antidepressant dosage range as tolerated (initial worsening of anxiety may be seen when treatment is started. (2)

2- The optimal duration of treatment should be at least one year. (2)

3- Effective treatment of GAD may prevent the development of major depression. (2)

4- Benzodiazepine can be used in crisis intervention and for short term, 2-4 weeks with close observation and caution for the possibility of addiction.

As some Anxiety disorders are more common and challenging, we will discuss in detail the management of Generalized Anxiety Disorder, Panic disorder and Social Anxiety disorder which are the most diagnoses seen in regular practice.

• Generalized Anxiety Disorder:

Generalized anxiety disorder (GAD) is a common and debilitating disorder. This is exacerbated further by the high prevalence of comorbidity with various psychiatric disorders and also general medical issues, both of which contribute to a complicated clinical presentation (16)

Clinical pearls:

- ✓ Worry that is extreme and uncontrollable.
- ✓ Agitation, irritation, and motor tension.
- ✓ Physical (somatic) symptoms (e.g., hyperventilation, tachycardia and sweating).
- ✓ GAD is usually associated with major depression, panic disorder, or obsessive-compulsive disorder (OCD).
- ✓ The 12-month prevalence is 1.7–3.4%.

Maintenance treatment	Category	Drug option	comments
First line treatment option	SSRI	e.g. Fluoxetine 20-80 mg/day Escitalopram 10-20mg/day	- Keep in mind that citalopram and all other medications that cause QTc prolongation have a relative-contraindication and should be used with caution and close monitoring to avoid arrythmia and Torsades de pointes. - SSRIs may aggravate symptoms at first. Therefore, It is suggested that patients begin with a smaller dose.
	SNRI	e.g. Venlafaxine 75-225mg/day Duloxetine 60-120 mg/day	- SNRI may aggravate symptoms at first. It is suggested that patients begin with a smaller dose. - Venlafaxine has a short half-life. Therefore, the patient should be educated about withdrawal symptoms.
Second-line drug treatment (less well tolerated or weak evidence base).	Tricyclic antidepressants	e.g. Imipramine 75-300 mg/day Amitriptyline 100-300mg/day	- TCA has a strong anticholinergic effect. -TCA can prolong QTc
	Beta-Blocker e.g. propranolol	Initiates at 40mg and titrate dose up to effect if needed.	It's suitable for somatic symptoms, especially tachycardia.
	Mirtazapine	15-45mg/day	Mirtazapine may induce morning sedation, which usually improves with sustained treatment, as well as an increase in appetite or weight gain.

Third line treatment option *These medications are supported by studies, but Not FDA approved. ((off-label))	**Valproic acid**	500-2250 mg / day	Only one double-blind, placebo-controlled randomized study that investigated the effectiveness of valproate in the treatment of anxiety disorders in 68 patients with generalized anxiety disorder reported that valproate significantly reduced anxiety symptoms compared to placebo (39)
	Quetiapine	50-300 mg /day	Antipsychotics have an adverse side effect profile (metabolic syndrome, extrapyramidal side effects and NMS), making them less favorable.
	Risperidone	0.5-1.5 mg / day	Antipsychotics have an adverse side effect profile (metabolic syndrome, extrapyramidal side effects and NMS), making them less favorable.

- ## Panic Disorder:

Panic attack is a sudden bout of acute terror that results in extreme physical reactions when there is no real risk or apparent reason. Although panic attacks are not life-threatening, they can be terrifying and substantially impact on one's quality of life. Treatment for panic attacks can be very effective.

To fulfill the diagnosis of panic disorder, patients must experience recurring panic attacks, with one or more attacks followed by at least one month of fear of another panic attack or severe maladaptive behavior related to the attack.

Clinical pearls:

- ✓ Sudden and unexpected bouts of extreme anxiety, generally lasting 30–45 minutes.
- ✓ Breathing problems and other autonomic symptoms.
- ✓ Fear of suffocation or death.
- ✓ Desire to escape as soon as possible.
- ✓ 12-month prevalence 1.8%.

Maintenance treatment	Category	Drug option	Comments
First line treatment option	**SSRI**	e.g. Fluoxetine 20-80 mg/day Escitalopram 10-20mg/day	- Keep in mind that citalopram and all other medications that cause QTc prolongation have a relative-contraindication and should be used with caution and close monitoring to avoid arrhythmia and Torsades de pointes. - SSRIs may aggravate symptoms at first. Therefore, It is suggested that patients begin with a smaller dose.
	SNRI	e.g. Venlafaxine 75-225mg/day Duloxetine 60-120 mg/day	Venlafaxine has a short half-life. Therefore, the patient should be educated about withdrawal symptoms.
Second-line treatment (less well tolerated or weak evidence base, no order of preference)	**Tricyclic antidepressants (TCA)**	e.g. Clomipramine 25–250mg/day Imipramine 25–300mg/day	A Bakker et al, meta-analysis indicated no variation in the effect size of SSRI vs. TCA in treating panic disorder, apart from adverse effect profile and drop rate, which were both worse for TCA. (11)
	Atypical Antidepressant	Mirtazapine 15-60 mg /day.	Although a meta-analysis reveals mirtazapine does not aid with panic symptoms, it does help with the anxiety that comes with this disorder.

- ## Social Anxiety Disorder (Social Phobia):

The fear of embarrassment and humiliation is a defining feature of social anxiety disorder. While normal social anxiety can help focus attention and prevent inappropriate behavior, the severe symptoms of social anxiety disorder can make it difficult to function or cause significant distress. In some social circumstances, it's natural to feel anxious. However, ordinary encounters create severe anxiety, self-consciousness, and shame for people with social anxiety disorder because they are afraid of being assessed negatively by others.

Clinical pearls:

- ✓ Extreme aversion to social circumstances, such as eating in public or giving a public speech.
- ✓ Afraid of being humiliated or embarrassed.
- ✓ Avoidant conduct, such as refusing to eat in restaurants.
- ✓ Anxiety expectation, such as feeling ill when entering a restaurant.
- ✓ 12-month prevalence 2.3%.

Maintenance treatment	Category	Drug option	Comments
First line treatment option	**SSRI**	e.g. Fluoxetine 20-80 mg/day Escitalopram 10-20mg/day	- Keep in mind that citalopram and all other medications that cause QTc prolongation have a contraindication. - SSRIs may aggravate symptoms at first. Therefore, It is suggested that patients begin with a smaller dose.
	SNRI	e.g. Venlafaxine 75-225mg/day Duloxetine 60-120 mg/day	In social phobia, there are open-label trials with the tricyclic antidepressants imipramine64 and clomipramine65, but no RCT.
Second-line treatment (less well tolerated or weak evidence base, no order of preference)	**Tricyclic antidepressants (TCA)**	e.g. Clomipramine25-250mg/day Imipramine 25–300mg/day	In social phobia, there are open-label trials with the tricyclic, showing its superiority in treating social phobia.
	Beta-blockers	e.g. Atenolol 25–100 mg/ day Propranolol 10 - 120 mg / day	Propranolol's effectiveness in the long-term treatment of anxiety disorders other than panic disorder is unproven. Propranolol is beneficial for people who have somatic symptoms associated with elevated adrenergic tone.

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