# Management of post-traumatic stress disorder: a review of anxiety disorders and PTSD

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## Abstract

Post-traumatic stress disorder (PTSD) and anxiety disorders are common psychiatric disorders worldwide, with a prevalence of 44.8 million cases in Africa. Their prevelance continues to increase over the years, with the major surge noticed during and after the COVID-19 pandemic. Emerging evidence indicates a strong association between anxiety disorders, including PTSD, with suicidal behaviour. Hence, they both have substantial impact on the individual and society. Thus, a comprehensive understanding of the management of these conditions is crucial. This review provides an overview of PTSD and anxiety disorders, focusing on their pharmacological and non-pharmacological management.

**Keywords:** Anxiety disorders, post-traumatic stress disorder, mental health, anti-anxiety treatment



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## Introduction

Mental disorders are characterised by clinically significant disturbances in an individual's cognition, emotional regulation, or behaviour. In 2019, one in every eight people, or 970 million people around the world were living with a mental disorder, with anxiety and depressive disorders being the most common.[1] The anxiety disorders are often chronic or recurrent and they impair quality of life and normal functioning of an individual. They include: generalised anxiety disorder, panic disorder with or without agoraphobia, specific phobias, agoraphobia, social anxiety disorder, separation anxiety disorder and selective mutism.[2] The prevalence of anxiety disorders for the year 2019 was 301.4 million cases globally, 44.8 million cases in Africa, with 2.15 million cases in South Africa.[3]

In 2020, the number of people living with anxiety and depressive disorders rose significantly because of the COVID-19 pandemic with estimates showing 26% and 28% increase respectively for anxiety and major depressive disorders in just one year.[1,4] It was estimated that there were additional 76.2 million cases of anxiety disorders globally due to COVID-19 in 2020.[5] Social isolation, the fear of uncertainty, being terminally sick, dying from COVID-19 complications, and/or losing loved ones to the pandemic were some of the contributors to the increase in anxiety disorders, not excluding the financial stress and unemployment that the pandemic led to.[5] These resulted in an increase in the anxiety disorders that people continue to struggle with to date. In 12 African countries, the lifetime prevalence of anxiety disorders ranged from 5.7% to 15.8%, while ranging from 14.7 to 38.8 % in South Africa.[6,7] With these increasing numbers of anxiety disorders, there is a need to clearly understand the management of these conditions. Hence, this review focused on pharmacological management of anxiety disorders and post-traumatic stress disorder (PTSD) with a brief cover on non-pharmacological management.

### *Epidemiology*

PTSD is a prevalent and complex psychiatric condition that arises in response to exposure to traumatic events, significantly impacting an individual's mental well-being.[8] Approximately 10% of people who experienced a traumatic event such as a serious accident, injury, sexual violence or threatened death events get PTSD.[9] From the countries that were affected by war during the years 1989-2019, the prevalence of PTSD was 26.5% among war survivors.[10,11] People living in sub-Saharan Africa (SSA) are disproportionately exposed to trauma and may be at increased risk for PTSD.[11] A study involving reports from ten SSA countries, including South Africa reported 22% prevalence of PTSD, that is due to domestic violence, road accidents, natural disasters, war and armed conflicts.[11] From a global study represented by 24 countries, COVID-19 survivors (15.45%), healthcare professionals (17.23%) and general population (17.3%) were reported to have experienced PTSD from the pandemic.[12] In South Africa, more women (28.5%) experience depression than men (24.4%) and more PTSD than men.[13,14]

Anxiety disorders affect an estimated 4% of the global population, encompassing approximately 301 million individuals.[3,15] This represents a more than 55% increase from 1990 to 2019, highlighting rising prevalence, incidence, and disability-adjusted life year (DALY) rates.[3] Prevalence is notably higher in high-income regions, with women being 1.66 times more likely to be affected than men.[3,16]

In South Africa, anxiety disorders were reported as the most prevalent lifetime disorders at 15.8% in a national survey conducted in 2009.[17] A more recent survey indicates that 17.8% of respondents showed probable anxiety.[18] Research in developing and underdeveloped regions remains limited, contributing to gaps in global understanding.[19]

### *Aetiology*

The aetiology of anxiety disorders remains unclear but is likely multifactorial, involving developmental, psychological, environmental, and genetic factors.[15] Anxiety can arise without identifiable triggers or in response to environmental and social stressors in adulthood, exacerbated by medical conditions, medications, and various substances, illustrating the complex interplay of biological, psychological, and social factors.[20]

Risk factors for anxiety disorders include a family history of anxiety disorders and female sex, both of which significantly increase susceptibility.[3,15,16,21] Children with at least one parent affected by anxiety disorders face a two- to fourfold higher risk and may develop symptoms earlier in life compared to peers without familial history.[15,21]

Early-life risk factors encompass parental interactions marked by over-involvement and negativity, as well as challenging peer relationships.[21] Epidemiologically, smoking and alcohol abuse correlate with anxiety disorders, although the nature of these associations remains bidirectional, and causality is not definitively established.[21]

Environmental stressors, such as traumatic events like prolonged illness, violence, bereavement, or abuse, are commonly linked to the onset of PTSD and anxiety disorders.[22] These stressors can significantly contribute to the development and exacerbation of anxiety symptoms.

### *Pathophysiology*

PTSD is a devastating psychiatric disorder that can strike individuals who have witnessed or experienced a traumatic event. Complex interplay between neurological, genetic and environmental factors plays a role in the pathophysiology of PTSD.[23] Studies using neuroimaging have shown changes in the brain regions of the amygdala, prefrontal cortex and hippocampus that are involved in the processing and regulation of fear. The development of PTSD has also been linked to dysregulated cortisol response caused by dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis.[24] Potential susceptibility genes for stress response and neurotransmitter modulation have been found through genetic investigations. PTSD manifests itself in three ways following exposure to trauma: reliving the incident in vivid memories, dreams, flashbacks, and/or psychologic distress; avoiding triggers that could trigger the trauma's memories or experiences; and being more aroused than usual.[1-3,25]

Various pathophysiological theories exist for anxiety disorders, including the noradrenergic model, which suggests hypersensitivity of the autonomic nervous system and over-reactivity to stimuli, mediated by norepinephrine release from the locus ceruleus activating both sympathetic and parasympathetic pathways. Dysregulated neurotransmitter activity such as norepinephrine, Gamma-aminobutyric acid (GABA), serotonin (5-HT), and dopamine contributes to anxiety symptoms.[26–28]

## Diagnosis

The diagnosis of PTSD and anxiety disorders involves a careful assessment of symptoms and their impact on the individual's life. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), PTSD is diagnosed when an individual has been exposed to actual or threatened death, serious injury, or sexual violence through direct experience, witnessing, or learning about an event affecting close family members or friends.[20] It's essential to exclude anxiety stemming from medical conditions or use of some substances/medications. Accurate diagnosis relies on thorough history-taking and clinical judgment due to the absence of specific laboratory tests.[20]

Anxiety disorders manifest with both psychological symptoms (e.g. excessive worry, mood changes, irritability) and physical symptoms (e.g. muscle tension, palpitations, shortness of breath).[20,21,29] Table I gives a summary of the diagnostic criteria and symptoms outlining distinctions between disorders such as generalised anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), and specific phobia.[20,21,29]

Neuroimaging studies implicate brain regions like the amygdala, anterior cingulate cortex, insula, and prefrontal cortex in anxiety disorders, revealing structural abnormalities and disrupted signalling mechanisms in disorders such as GAD, PD, and PTSD.[26–28]

Diagnosis in children often involves systematic clinical interviews with parents, caregivers, and sometimes teachers. However, these standardised methods are underutilised in clinical practice due to limited clinician training, time constraints, and prioritisation of physical symptoms over psychological ones.[20]

## Impact on quality of life

PTSD and anxiety disorders profoundly impact quality of life across multiple domains. Longitudinal studies consistently link anxiety and depression to declining quality of life across all age groups, with significant impacts observed in chronic conditions like chronic obstructive pulmonary disease (COPD).[30] Social anxiety disorder is particularly debilitating, leading to significant functional impairment and reduced overall well-being.[28] Generalised anxiety disorder (GAD) and depressive disorders (DD) contribute to dysfunctional thoughts that hinder goal attainment and fulfilment, resulting in substantial impairment in quality of life.[31] Individuals with anxiety disorders report significantly lower subjective perceptions of health, social relationships, occupation, and family life compared to those without such disorders.[32]

**Table I:** Summary of diagnostic criteria of PTSD and common anxiety disorders and their symptoms

| Disorder | Diagnostic criteria | Onset and course | Psychological symptoms | Physical Symptoms |
|---|---|---|---|---|
| **PTSD** | Exposure to actual or threatened death, serious injury, or sexual violence. Presence of intrusive symptoms, avoidance, negative alterations in cognitions and mood, and marked alterations in arousal and reactivity, lasting more than one month and causing significant distress or impairment. | Symptoms typically begin within three months of the traumatic event but can have a delayed onset | Intrusive memories and distressing dreams related to the traumatic event. Flashbacks, intense distress at reminders of the trauma | Sleep disturbances, hypervigilance, exaggerated startle response, and problems with concentration. Physical reactions (e.g., sweating, increased heart rate) when reminded of the traumatic event |
| **Generalised Anxiety Disorder (GAD)** | Excessive anxiety and worry about multiple activities or events, occurring more days than not for ≥ 6 months. | Gradual onset, typically around age 21, chronic course, high comorbidity with depression | Excessive anxiety, worries difficult to control, feeling keyed up, trouble concentrating | Restlessness, fatigue, muscle tension, sleep disturbance, irritability |
| **Panic Disorder** | Recurrent panic attacks. ≥ 1 attack followed by ≥ 1 month of persistent worry about additional attacks or their consequences, or maladaptive behaviour changes. | Series of unexpected attacks, chronic course, high risk for suicide attempts | Depersonalisation, derealisation, fear of losing control or dying | Abdominal distress, chest pain, chills, dizziness, choking, nausea, palpitations, sweating, tachycardia, trembling |
| **Social Anxiety Disorder (SAD)** | Marked, persistent (≥ 6 months) fear or anxiety about social situations where they may be scrutinised. Fear of negative evaluation. | Onset in mid-teens, chronic with 20-year duration, high comorbidity with mood and substance use disorders | Fear of scrutiny, negative evaluation, immediate panic attacks | Blushing, "butterflies", diarrhoea, stumbling over words, sweating, tachycardia, trembling |
| **Specific Phobia** | Marked, persistent (≥ 6 months) fear or anxiety about a specific object or situation. | Avoidance of feared object or situation with adjustment to activity restrictions | Fear of a specific object or situation | Symptoms absent when not exposed to the feared object |

## Management

According to Marti et al. there is a large information treatment guideline being produced worldwide to support health professionals in clinical decision-making on PTSD and anxiety.[33] Even so, it is vital for health professionals to be able to recognise which quality guidelines can be the most trusted. The review recommended universally SSRIs followed by TCAs to be accepted as first-line pharmacological treatment of PTSD in clinical guidelines.[33,34] However, they've stated that these recommendations are not one size fit all, given examples: cost, psychotherapy may not be accessible in the rural areas, patients with comorbidities and rights on the choice of treatment.

The goals of treatment in PTSD and anxiety disorders is to:

- Provide symptomatic relief
- Shorten duration of illness
- Prevent relapse
- Improve quality of life

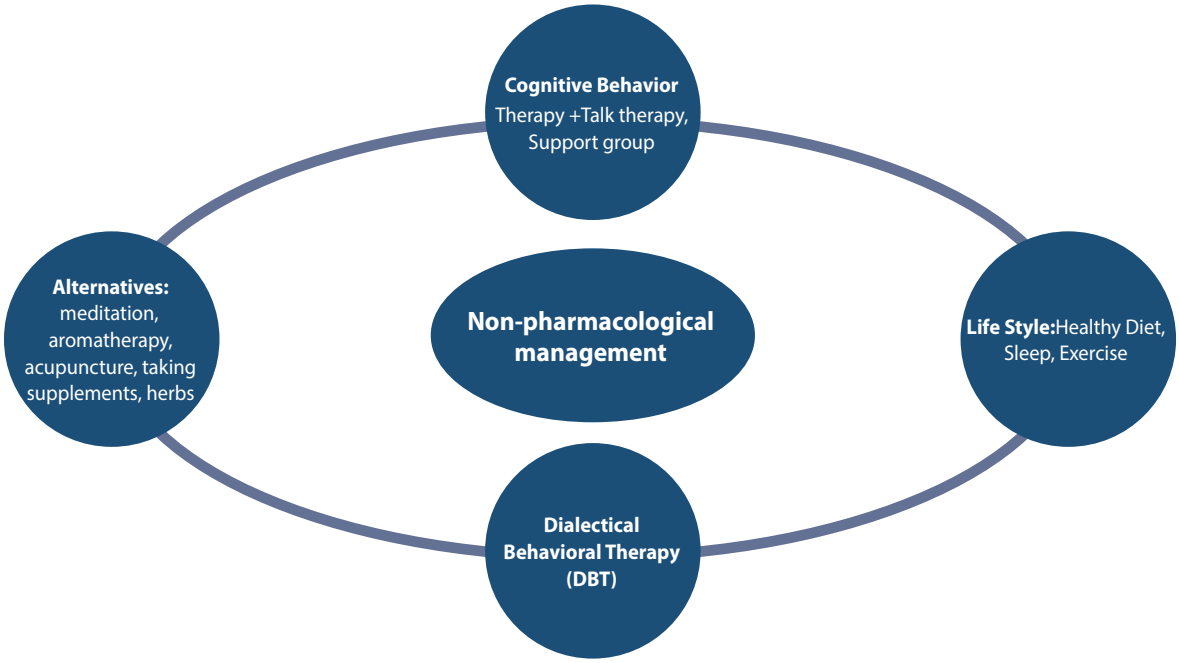


**Figure 1:** Non-pharmacological management of Post Traumatic Stress Disorder and Anxiety Disorders

### *Non-pharmacological management*

Non-pharmacological interventions play a crucial role in the management of PTSD and AD. Techniques include Mindfulness-Based Therapies, Cognitive Behavioural Therapy, Eye Movement Desensitisation as well as Reprocessing, Lifestyles, Alternatives and Dialectical Behavioural Therapy (DBT). These approaches offer alternatives to medication-based treatment and provide hope for individuals seeking options for managing and recovering from conditions that significantly affect their quality of life.[35,36] The non-pharmacological treatment of PTSD and AD is illustrated in Figure 1.

## Pharmacological management

There are different classes of drugs that help in the management of PTSD and anxiety disorders.

#### *1. Selective serotonin reuptake inhibitors (SSRIs)*

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) have been approved by various regulators around the world for PD, GAD and SAD. SSRIs and SNRIs are both first-line treatments for PD, GAD, and SAD, PTSD, and obsessive-compulsive disorder.[5,29]

The primary mechanism of this class of drugs is selective inhibition of the presynaptic serotonin transporter (SERT) pump resulting in increased concentrations of serotonin.[5]

As a class, SSRIs are considered first-line pharmacotherapy agents for anxiety disorders due to their overall levels of safety, efficacy and tolerability.[5] They are relatively safe in overdose and lack the monitoring requirements often needed with other psychotropic medications.[5]

Common adverse effects of SSRIs include gastrointestinal effects (nausea, vomiting, and changes in bowel habit), sedation, sexual dysfunction, and increased risk of bleeding.[5]

#### *2. Serotonin-noradrenaline reuptake inhibitors (SNRIs)*

SNRIs inhibit both SERT and the noradrenaline transporter (NET), increasing extracellular concentrations of serotonin and noradrenaline.[37] The adverse effect profile of both agents is broadly similar to SSRIs. Additional adverse effects seen are related to the increased noradrenergic stimulation: principally dry mouth, increased sweating, urinary retention, blurred vision, and constipation.[5]

#### *3. Tricyclic antidepressants (TCAs)*

The tricyclic antidepressants (TCAs), act primarily through SERT and NET inhibition, increasing extracellular concentrations of serotonin and noradrenaline. However, different TCAs inhibit the two transporters to differing degrees. Many TCAs have additional antagonism at α1-adrenoceptors, 5-HT2A, and 5-HT2C receptors, H1 receptors, and muscarinic acetylcholine receptors.[37] They were one of the first classes of medications used for anxiety disorders.[10,38] Despite comparable efficacy to SSRIs, they are now less frequently prescribed due to concerns about side effects including weight gain, dry mouth, sedation, urinary hesitancy or retention, arrhythmias, and risk of mortality with overdose.[38]

#### *4. Monoamine oxidase inhibitors (MAOIs)*

Monoamine oxidase inhibitors (MAOIs) are also older antidepressant medications which are now typically used only as a third-line option because of side effects and dietary restrictions. They are not FDA-approved for anxiety disorders but may be considered in patients with SAD who are non-responsive to SSRIs.[39]

Buspirone, a 5-HT1A partial agonist classified under the azapirones, is FDA- approved for use in anxiety, and is commonly used as an adjunctive treatment with SSRIs or SNRIs primarily for GAD.

#### *5. Mixed antidepressants*

Mirtazapine is the only drug within this category due to its broad pharmacological action on different receptors. It causes antagonism of the alpha-2 adrenergic receptor, postsynaptic blockade of 5-HT2 and 5-HT3 receptors, and antagonism of histamine-1 (H1) receptors. The principal adverse effects of mirtazapine are weight gain and sedation (secondary to H1 receptor antagonism), although the latter appears to be less marked at higher treatment doses.[39]

#### *6. Gamma aminobutyric acid (GABA)*

Gabapentinoids, such as gabapentin and pregabalin, are derivatives of gamma-aminobutyric acid (GABA) and demonstrate a high affinity for the α2δ subunit of voltage-gated calcium channels, disrupting their function. Several randomised control trial (RCTs) support the efficacy of pregabalin in the treatment of GAD.[40] Pregabalin is generally well tolerated with common adverse effects including drowsiness, dizziness, vertigo, and weight gain.[5]

Benzodiazepines have been a longstanding treatment for anxiety and are still among the most widely prescribed class of psychiatric medications in the world. Benzodiazepines are no longer considered first line monotherapy for PD or other anxiety disorders but can be used in the short-term on either a standing or as-needed basis for PD, GAD, and SAD in conjunction with SSRIs and SNRIs.[5]

#### *7. Antihistamines*

Hydroxyzine is the most studied antihistamine for anxiety and the only antihistamine which is FDA-approved for use in anxiety.[29] It is a histamine-1 receptor (H1) blocker that can be used as an alternative to benzodiazepines for anxiety, panic attacks, and insomnia, in both inpatient and outpatient settings.

Beyond its antihistaminic activity, hydroxyzine is also prescribed as a psychotropic medication for its tranquiliser and sedative properties, as it is a weak antagonist of the serotonin 5-HT2A, dopamine D2, and α1-adrenergic receptors.[41] The weak anti-serotonergic effects of hydroxyzine make it useful as an anxiolytic with reduced activity in certain key subcortical regions, such as the reticular formation and limbic system.

Hydroxyzine is a first-generation antihistamine, which means it crosses the blood–brain barrier easily and exerts effects on the central nervous system (which explains it sedative and anxiolytic effects). It is a piperazine derivative, chemically unrelated to phenothiazine.

Other main side effects due to the other receptors hydroxyzine works on include dry mouth, nausea, vomiting, diarrhoea, constipation, dysuria, urinary retention, increased appetite, and tachycardia.

### *8. Alpha- and beta-adrenergic agents*

Many of the symptoms of performance anxiety, including tremor and palpitations, are brought on by an increase in the release of adrenaline and norepinephrine from the sympathetic nervous system and adrenal medulla, and medications that block adrenoceptors, such as clonidine and propranolol, minimise or eliminate these symptoms.

Stress-related norepinephrine release and compensatory downregulation of beta-adrenergic receptors in the heart and peripheral vessels appear to play a role in the physiological reactions of anxiety. In PTSD, the noradrenergic system is of key importance in modulating memory processes, and it has been found that stimulation of β-ARs facilitates the reconsolidation of emotional memory.

Clonidine is an alpha-2 adrenergic receptor agonist, FDA-approved for the treatment of hypertension.[41] It reduces the release of norepinephrine and has been suggested as a treatment for PTSD.[42]

Propranolol is a non-cardio selective beta-adrenergic antagonist that is FDA-approved for multiple indications including hypertension, angina, atrial fibrillation and arrhythmias, migraine prophylaxis, and essential tremor.[29] Although it is not approved for any psychiatric indications, propranolol is useful in lowering emotional arousal and controlling stage fright. Propranolol has been shown to interfere with memory reconsolidation.

### *9. Antipsychotics*

Antipsychotics, most of which are dopamine-2 (D2) receptor antagonists, have been utilised on an off-label basis for multiple indications other than psychosis including anxiety. Atypical antipsychotics are effective against negative and cognitive symptoms, unlike typical antipsychotics, which are effective only against positive symptoms of schizophrenia.[5] There is currently only one antipsychotic, trifluoperazine, a first-generation antipsychotic (FGA), which is FDA-approved for the treatment of anxiety. However, it is no longer used in clinical cases.

Table II: Available PTSD and anxiety classes with examples and common adverse effects and recommended doses in South Africa.

| Class of medicine | Common adverse effects | Examples |
|---|---|---|
| Selective Serotonin Receptor Inhibitors: | Gastrointestinal effects (nausea, vomiting, and changes in bowel habits), sedation, sexual dysfunction, and increased risk of bleeding | Fluoxetine<br>Sertraline<br>Citalopram<br>Escitalopram<br>Paroxetine<br>Paroxetine ER<br>Fluvoxamine |
| Serotonin Norepinephrine Receptor Inhibitors: | Dry mouth, increased sweating, urinary retention, blurred vision, and constipation | Duloxetine<br>Venlafaxine (XR)<br>Desvenlafaxine |
| Tricyclic Antidepressants: | Weight gain, dry mouth, sedation, urinary hesitancy or retention, arrhythmias | Clomipramine<br>Imipramine<br>Desipramine<br>Nortriptyline |
| Mixed antidepressants: | Weight gain and sedation | Mirtazapine |
| GABAergic drugs: | Drowsiness, dizziness, vertigo, and weight gain | Pregabalin<br>Gabapentin |
| Benzodiazepines: | Sedation, drowsiness, and mental slowing) and psychomotor impairment (including when driving) | Clonazepam<br>Alprazolam<br>Lorazepam<br>Chlordiazepoxide<br>Oxazepam |
| Antihistamines | Drowsiness, dry mouth, gastrointestinal upset, stomach pain | Hydroxyzine |
| Alpha- and Beta-adrenergic agents | Bradycardia, orthostatic hypotension, fatigue, dizziness, headaches | Propranolol |
| Antipsychotics | Weight gain, dizziness, hyperlipidaemia, diabetes mellitus, QTc prolongation, extrapyramidal side effects | Aripiprazole Olanzapine |

There is reasonable concern about the short- and long-term risks of using antipsychotics in anxiety disorders. First, there are limited studies to date in other anxiety disorders such as SAD and PD. Second, it is unclear whether patients receive appropriate psychoeducation about the risks of tardive dyskinesia, extrapyramidal symptoms, neuroleptic malignant syndrome, weight gain, and metabolic syndrome.[12] Table II gives a summary of the available drug options in South Africa to treat PTSD and AD

## Barriers to care

Barriers to accessing care for anxiety disorders are multifaceted and pervasive. Common impediments include inadequate awareness about the effectiveness of treatments, insufficient investment in mental health services, shortages of trained healthcare professionals, and enduring social stigma.[15,43] Many individuals also opt for self-management or perceive available treatments as ineffective, contributing to low treatment uptake rates.[44]

These challenges persist even in high-income countries, prompting calls for national initiatives aimed at enhancing public awareness, reducing stigma, and fostering supportive social environments to bridge the treatment gap.[15,44] Efforts to address these barriers are essential for ensuring that individuals with anxiety disorders receive timely and effective care to improve their overall well-being.

## Conclusion

PTSD and anxiety disorders negatively affect the quality of life and require proper timely interventions to promote well-being. These conditions affect different biological systems, and their treatment includes combination of medicines and psychotherapy. This review highlights the importance of both pharmacological and non-pharmacological treatments in alleviating symptoms, improving functioning, preventing relapse, and enhancing the quality of life for affected individuals. Ongoing research and increased investment in mental health services are crucial to bridging the treatment gap and providing holistic care to those struggling with these debilitating disorders.

### *Conflict of interest*

The authors declares that there are no conflicts of interest

### *Authors contribution*

All authors drafted and reviewed the manuscript.

### *Ethical approval*

Ethical approval was not required.

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