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EDITORIAL

Generalised Anxiety Disorder and Depression: Contemporary Treatment Approaches

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Key Summary Points

Why carry out this review?

Generalised anxiety disorder (GAD) and major depressive disorder (MDD) form part of a large group of prevalent psychiatric disorders, and are frequently comorbid.

These manuscripts describe presentations from a virtual symposium titled “GAD and Depression: Contemporary Treatment Approaches” as part of the Industry Science Exchange sessions that took place as at the European College of Neuropsychopharmacology 33rd Congress in September 2020.

What was learned from the review?

Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors are considered first-line therapy in patients with GAD, but agents with a different mechanism of action may also be considered in those who do not respond to or tolerate these therapies.

Patients with MDD with symptoms of GAD, also referred to as anxious depression, should be managed with an antidepressant that has anti-anxiety effects.

Greater recognition of anxious depression is needed as this condition is often accompanied by increased suicidality and the need for more robust treatment.

EDITORIAL

Anxiety and depression form a large group of interrelated, overlapping psychiatric disorders whose precise taxonomy and terminology can at first be confusing. In this supplement, we will mainly discuss generalised anxiety disorder (GAD), major depressive disorder (MDD) and anxious depression. Figure 1 shows how GAD and MDD fit into the overall disease classifications of anxiety and depressive disorders, as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition; commonly referred to as DSM-5) [1].

Current diagnostic criteria for GAD and MDD are shown in Table 1. GAD and MDD are prevalent, debilitating illnesses that frequently coexist [2]. In severe cases, GAD may be associated with disabling symptoms, social and occupational impairment, an increased risk of suicidality, and reportedly low rates of treatment response [3, 4]. In patients with a major depressive episode, coexisting symptoms of anxiety (or ‘anxious depression’) increase the severity of depression, worsen functional impairment, reduce quality of life, and add to the economic burden [5]. Although there are now effective treatments for GAD, many patients do not respond, are unable to tolerate them, or experience discontinuation symptoms when treatment is stopped [6]. Additionally, there are effective treatments for anxious depression, but these have been less thoroughly researched [7].

At a population level, the burden of human disease (or ‘health loss’) can be measured in terms of disability adjusted life-years (DALYs). The total number of DALYs for a given population has two components: premature death, which is quantified as the number of years of life lost due to disease or injury; and morbidity, which is quantified as the number of years lived with disability (YLD) [8]. YLD is particularly relevant to mental illnesses such as GAD and MDD. Data from the Global Burden of Disease Study 2019 show that the societal impact of anxiety and depression is extremely high, in both absolute and relative terms. Both disorders are associated with very significant global health losses, predominantly due to high numbers of associated YLDs (Table 2) [9, 10]. Importantly, these losses are seen globally, occurring in low- and middle-income countries, as well as in wealthier nations [10]. Moreover, both disorders are prominent contributors to global DALYs among adults of working age [9], a finding with considerable socioeconomic implications. In the USA, MDD was the second-largest contributor to YLDs in 2010, while

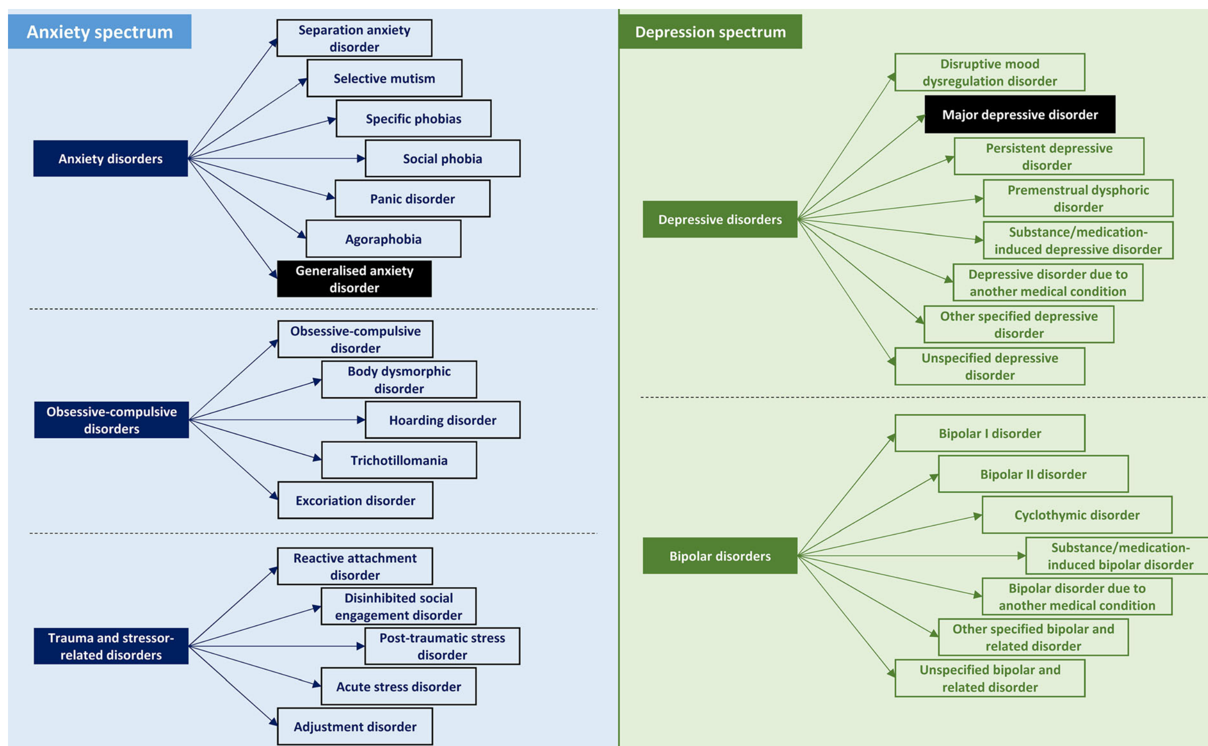

Fig. 1 Classification of anxiety and depressive disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) [1]. Generalised anxiety disorder and major depressive disorder are indicated in black boxes with white text

anxiety disorders together were the fifth largest [11]. The percentage of global YLDs attributable to depression and anxiety remained relatively stable between 1990 and 2019 [10]; this is despite considerable ongoing research, the availability of numerous effective pharmacotherapies, and the growth and diversification of psychological treatment options.

Traditionally, clinical psychiatry has emphasised treatment rather than prevention and focused on manifestations rather than causes. Moving forward, should psychiatry shift its focus to identifying at-risk individuals and intervening earlier, with the objectives of preventing illness or reducing its severity and duration? Screening for at-risk individuals or possible causes of GAD (e.g. excessive perceived threat), as well as symptoms and signs of GAD in patients with or without MDD, could form part of such a strategy, given that GAD often has earlier onset than MDD and may increase vulnerability to developing MDD. Additionally, there is growing interest and research into the neurobiological mechanisms of GAD, which may ultimately allow for the development of targeted treatments. Evolutionary medicine may also offer clues as to how we approach GAD and MDD in the future, e.g. by viewing anxiety and depression as adaptive responses to particular circumstances, which may at times be excessive, analogous to the current understanding of allergies based on adaptive immune responses, which at times are disproportionate.

For now, we have effective pharmacotherapies both for GAD and for anxiety associated with MDD. In both conditions, treatment has the potential to decrease or relieve symptoms, improve or restore functioning, and increase health-related quality of life. From a public health point of view, the cost-effectiveness of

Table 1 Diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), for generalised anxiety disorder and major depressive disorder [1]

Generalised anxiety disorder	Major depressive disorder
All the features listed below must be present in order to make a diagnosis of generalised anxiety disorder	At least five of the following symptoms must be present nearly every day during a 2-week period:
Excessive anxiety and worry about various events have occurred more days than not for at least 6 months	Core symptoms ($\geq$ 1 required for diagnosis):
The person finds it difficult to control the worry	Depressed mood most of the day
The anxiety and worry are associated with at least three of the following six symptoms (only one symptom is required in children):	Anhedonia or markedly decreased interest or pleasure in almost all activities
Restlessness or a feeling of being keyed up or 'on edge'	Additional symptoms:
Being easily fatigued	Clinically significant weight loss or increase or decrease in appetite
Having difficulty concentrating	Insomnia or hypersomnia
Irritability	Psychomotor agitation or retardation
Muscle tension	Fatigue or loss of energy
Sleep disturbance	Feelings of worthlessness, or excessive or inappropriate guilt
The anxiety, worry, or associated physical symptoms cause clinically significant distress or impairment in important areas of functioning	Diminished ability to think or concentrate, or indecisiveness
The disturbance is not due to the physiological effects of a substance or medical condition	Recurrent thoughts of death or suicidal ideation
The disturbance is not better accounted for by another mental disorder	The symptoms cause clinically significant distress or impairment in functioning
	Symptoms are not due to a medical/organic factor or illness

treatments for GAD and MDD is worth emphasising. In this supplement, we review the evidence base that supports treatments for GAD in 2021—both pharmacological and non-pharmacological—with a particular focus on recent meta-analyses and emerging treatments. We will also explore how our understanding of the relationship between anxiety and depression has evolved, and summarise current best practice in the management of anxious depression.

Table 2 Years lived with disability (YLD) due to depression and anxiety, expressed in absolute numbers, number per 100,000 population, and as a percentage of all YLDs [9, 10]

Region	Depressive disorders				Anxiety disorders			
	Total YLDs (thousands)	YLDs per 100,000	% of all YLDs	Rank cause	Total YLDs (thousands)	YLDs per 100,000	% of all YLDs	Rank cause
World	54,215	738	7.5	1	24,621	335	3.4	6
Low- and middle-income countries								
African region	7229	731	7.9	2	2639	267	2.9	7
Eastern Mediterranean region	4049	685	6.9	2	2093	354	3.6	7
European region	3517	859	8.1	2	1239	302	2.9	8
Region of the Americas	5106	844	9.3	1	3433	567	6.2	3
Southeast Asian region	13,967	724	7.0	2	5522	286	2.8	9
Western Pacific region	10,525	640	7.2	2	4506	274	3.1	8
High-income countries	9608	839	7.9	2	5061	442	4.2	4

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