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Primer

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Major depressive disorder

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Abstract

Major depressive disorder (MDD) is characterized by persistent depressed mood, loss of interest or pleasure in previously enjoyable activities, recurrent thoughts of death, and physical and cognitive symptoms. People with MDD can have reduced quality of life owing to the disorder itself as well as related medical comorbidities, social factors, and impaired functional outcomes. MDD is a complex disorder that cannot be fully explained by any one single established biological or environmental pathway. Instead, MDD seems to be caused by a combination of genetic, environmental, psychological and biological factors. Treatment for MDD commonly involves pharmacological therapy with antidepressant medications, psychotherapy or a combination of both. In people with severe and/or treatment-resistant MDD, other biological therapies, such as electroconvulsive therapy, may also be offered.

Sections

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Introduction

Major depressive disorder (MDD) is a common mental disorder that affects ~185 million people globally[1]. Manifestations of MDD include depressed mood, reduced interest or pleasure in previously enjoyable activities, and recurrent thoughts of death. Individuals with MDD also experience stigma[2], higher rates of physical comorbidities, such as cardiovascular disease, obesity and type 2 diabetes mellitus, and increased risk of negative outcomes related to education[3], employment[4] and personal relationships[5,6].

MDD is a complex disorder that seems to be caused by a combined effect of genetic[7,8], environmental (such as poverty, recent negative life events and childhood maltreatment)[9], psychological (such as cognitive patterns)[9] and biological (such as inflammatory[10] and monoamine pathways[11]) factors.

Diagnostic criteria for MDD are found in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision (DSM-5-TR) and the International Classification of Diseases 11th Revision (ICD-11)[12,13]. Recommended and commonly used treatments for depression typically involve antidepressant medications (such as selective serotonin reuptake inhibitors (SSRIs)) and/or psychotherapy (such as cognitive behavioural therapy (CBT)). Other biological therapies such as electroconvulsive therapy (ECT) can be used in people with severe and/or treatment-resistant MDD[14]. Several newly developed and emerging interventions are being evaluated in clinical trials or have been introduced into clinical practice, including biological interventions (such as transcranial magnetic stimulation (TMS), ketamine or psychedelics) and lifestyle interventions (such as diet modification and exercise)[15,16].

This Primer summarizes the epidemiology, biological and environmental mechanisms, management, and prevention of MDD and provides an overview of emerging research and the effect of MDD on daily functioning and quality of life (QOL). We prioritized evidence from systematic reviews, meta-analyses, network meta-analyses, and umbrella reviews of randomized controlled trials (RCTs) and observational studies, where appropriate. Although MDD overlaps with other mental health disorders, such as bipolar disorder, adjustment disorder, dysthymia and comorbid depression (which have been covered in other Primers[17–19]), this Primer focuses specifically on MDD as the primary diagnosis.

Epidemiology

Prevalence

The estimated prevalence of MDD varies markedly depending on the study design and measures used. For instance, globally, lifetime prevalence was ~10% in the WHO World Mental Health Survey[20], which was based on retrospective assessments, thereby likely underestimating true prevalence owing to under-reporting and recall bias[21]. Prospective studies have suggested a lifetime prevalence of >30%[21]. Studies of shorter time frames are less affected by survival and recall bias, with systematic reviews[22] and multi-national studies[23] finding an estimated 12-month prevalence of 4–5% globally.

The prevalence of MDD varies between countries although, in general, prevalence is only modestly different in high-income countries (HICs) and low-income countries (LICs)[1] (Fig. 1). Prevalence is highest in Greenland and Greece and lower values are observed in countries and regions in South-East Asia and Oceania such as Vietnam and the Solomon Islands[1] (Fig. 2). However, whether these differences are 'true' differences in prevalence is unknown as prevalence can be influenced by other factors such as cultural differences in acknowledgement and recognition of mental ill-health, stigma, and methodological factors[1,23].

The prevalence of MDD is almost twice as high in women than in men across the world and remains relatively consistent across adulthood[1,24]. The sex difference in prevalence could be attributable to differences in biopsychosocial factors, including biological and developmental factors (such as genetics and hormonal differences), psychological factors (such as differences in ruminative response style and self-conscious emotions), and environmental factors (such as societal gender inequities)[24].

Course of disease

MDD typically emerges in early adulthood, with data from both HICs and LICs observing first onset around 20–25 years of age[25,26]. Of note, studies of the course of illness are affected by study-level factors such as selection bias. In community surveys, the median duration of depressive episodes (low mood and depression symptoms for at least 2 weeks) is 2–6 months and >70% of episodes subside within 12 months[27], with many individuals remaining in remission. By contrast, in studies within primary and secondary mental health-care settings, approximately 34–48% of patients have persistent illness (that is, an episode lasting >12 months) and recurrence is very high (up to 85% in some studies)[25]. Factors associated with longer duration of depressive episodes include depression severity and longer depression duration before treatment, whereas better physical and mental functioning before depression onset may predict shorter duration[27].

Mortality

MDD is associated with premature mortality[28], of which a large proportion is due to higher rates of comorbid diseases in people with MDD compared with the general population[29]. Suicide is also a key contributing factor to this increased mortality. Indeed, MDD is the leading cause of years of life lost to suicide[30], increasing the risk of death by suicide almost 20 times compared with that in those without MDD (RR 19.7, 95% CI 12.2–32.0)[31]. MDD is also associated with higher risk of suicidal ideation, planning and attempts[32]. This risk might be further increased in MDD that presents with psychotic features such as delusions or hallucinations[33]. Other risk factors for suicide include male sex, history of previous suicide attempts, more severe depressive symptoms, and comorbid anxiety or substance use disorders[34].

Mechanisms/pathophysiology

Much of the mechanistic discussion in MDD, and psychiatry in general, has been dominated by the monoamine hypothesis, whereby central deficiencies in monoaminergic neurotransmitters (such as serotonin, noradrenaline and dopamine) are thought to be, at least partially, responsible for MDD. This theory was initially developed owing to observations that medications that modulated serotonin and noradrenaline levels influenced mood. However, the time delay between the administration of antidepressants that modulate monoamine pathways within hours and clinical effect on MDD, which can take weeks, along with high variability in treatment response and clinical presentation of people with MDD, suggest that other mechanisms are involved[35].

MDD is a complex disorder; both aetiological factors and molecular and cellular mechanisms are involved in the onset and continuity of MDD. Involved aetiological factors include genetic and environmental factors whereas involved mechanisms include alterations in brain

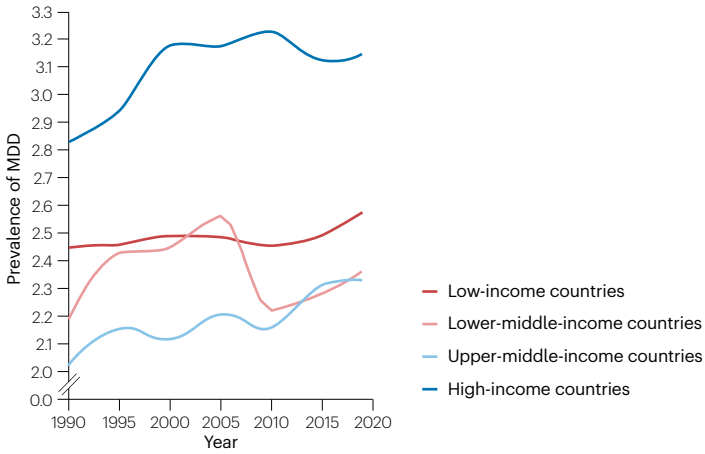

Fig. 1 | Prevalence of MDD across global regions over time. World Bank income classifications. Although both high-income countries and low-income and middle-income countries (categorized using World Bank income classifications) report a prevalence of major depressive disorder (MDD) within 2–3.1%, high-income countries report a generally higher prevalence of MDD, with a lower prevalence reported in lower-middle-income and upper-middle-income countries. Reprinted with permission from ref. 1, IHME.

structure and function, inflammation, the gut–brain axis, and the hypothalamus–pituitary–adrenal (HPA) axis.

In general, the combination of biological susceptibility and environmental risk and protective factors determines risk of MDD. However, discrete risk or protective factors for MDD account for only a small proportion of risk[25,36]. Indeed, one study identified 37 risk factors, each of very small variance and few operative in each person[37]. Of note, these factors are generally non-specific for MDD and the presence of these risk factors does not always result in MDD. Most conceptualizations of MDD that focus on the interaction of biological susceptibility and risk and protective factors are variants of the so-called vulnerability–stress model, which states that genetic, psychological or biological vulnerabilities predispose to MDD but require individual exposure to certain environmental stressors to manifest as MDD[25]. Evidence of gene–environment correlation indicates that vulnerability and stressors are not independent. In addition, the degree of vulnerability and stress exposure are likely related: individuals of high vulnerability might only require exposure to a mild stressor for MDD to develop, whereas individuals of low vulnerability might only develop MDD if exposed to severe stressors.

Genetics and epigenetics

Offspring of individuals with MDD have a 35–40% risk of developing MDD by early adulthood, which is double the risk found in offspring of parents without MDD[7,8]. Genetic and within-family environmental factors (such as high educational status and economic security) provide roughly equal contributions to the familial risk of MDD[38]. The estimated heritability of MDD is ~37%, which is lower than the heritability of most other mental disorders[39]. Owing to the substantial heritability of affective disorders, assessing for family history of MDD and related disorders is important as part of clinical assessment and formulation in those with suspected MDD.

Large-scale molecular genome-wide association studies (GWAS) involving up to 500,000 persons with MDD (diagnosed via electronic records, structured diagnostic interview or self-report) and >3 million controls have illustrated that very small effects (OR <1.05 for individual variants) of several common genetic variants underlie the genetic risk of MDD[40,41]. These studies have estimated a heritability of ~8.4% for MDD based on single nucleotide polymorphisms. In contrast to some psychiatric disorders (such as schizophrenia), there is limited replicated evidence of a major role of structural variation or rare genetic variability in the overall heritability of MDD[42].

The established genome-wide significant findings from GWAS over-represent genes encoding proteins involved in synaptic structure and function, neuron growth, neurotransmission and response to stimuli, and inflammation. For example, *DRD2* (encoding the dopamine receptor D2 subtype), *CELF4* (coordinating synaptic function in excitatory neurons) and *ELAVL2* (encoding a protein that regulates gene expression pathways in neurodevelopment) are significant findings from multiple GWAS[40,41].

Interestingly, GWAS have revealed a high genetic correlation (r_G >0.6) among some mental disorders and relevant personality traits, such as neuroticism, subjective well-being and anxiety[43], and moderate correlations for other disorders such as attention-deficit/hyperactivity disorder, bipolar disorder and schizophrenia. This moderate/high correlation across many mental disorders suggests shared genetic risks and might explain the high comorbidity between various mental disorders[44,45]. Shared genetic vulnerability also extends to cardiometabolic traits, including body mass index, coronary artery disease and type 2 diabetes mellitus[46]. However, there is limited evidence for genetic correlation between MDD and neurological disorders such as Alzheimer disease[44].

A further dimension to genetic risk for MDD is gene–environment interactions, whereby genetic factors related to MDD can be influenced by environmental factors specific to the individual, of which childhood trauma and life adversity are some of the most well studied[47]. Epigenetic mechanisms might mediate gene–environment interactions. Indeed, some epigenetic markers related to MDD and prominent risk factors for MDD (such as childhood trauma) have been identified in blood of people with MDD as well as in post-mortem brain samples of people with MDD[48–50]. However, epigenome-wide screenings have not yet included sufficiently large samples to allow definitive conclusions. Of note, several compounds that target epigenetic pathways, for example, histone deacetylases and DNA methyltransferases, have demonstrated efficacy in animal models of MDD; however, human intervention studies are lacking[51].

Environmental risk and protective factors

Several environmental risk and protective factors for MDD have been identified. These factors encompass demographic, psychological, sociocultural and community, behavioural, and health factors[9] (Table 1). Protective factors increase resilience (the ability to maintain or regain mental health in the face of adversity). The effect of risk and protective factors can be context-specific and time-specific. Moreover, these

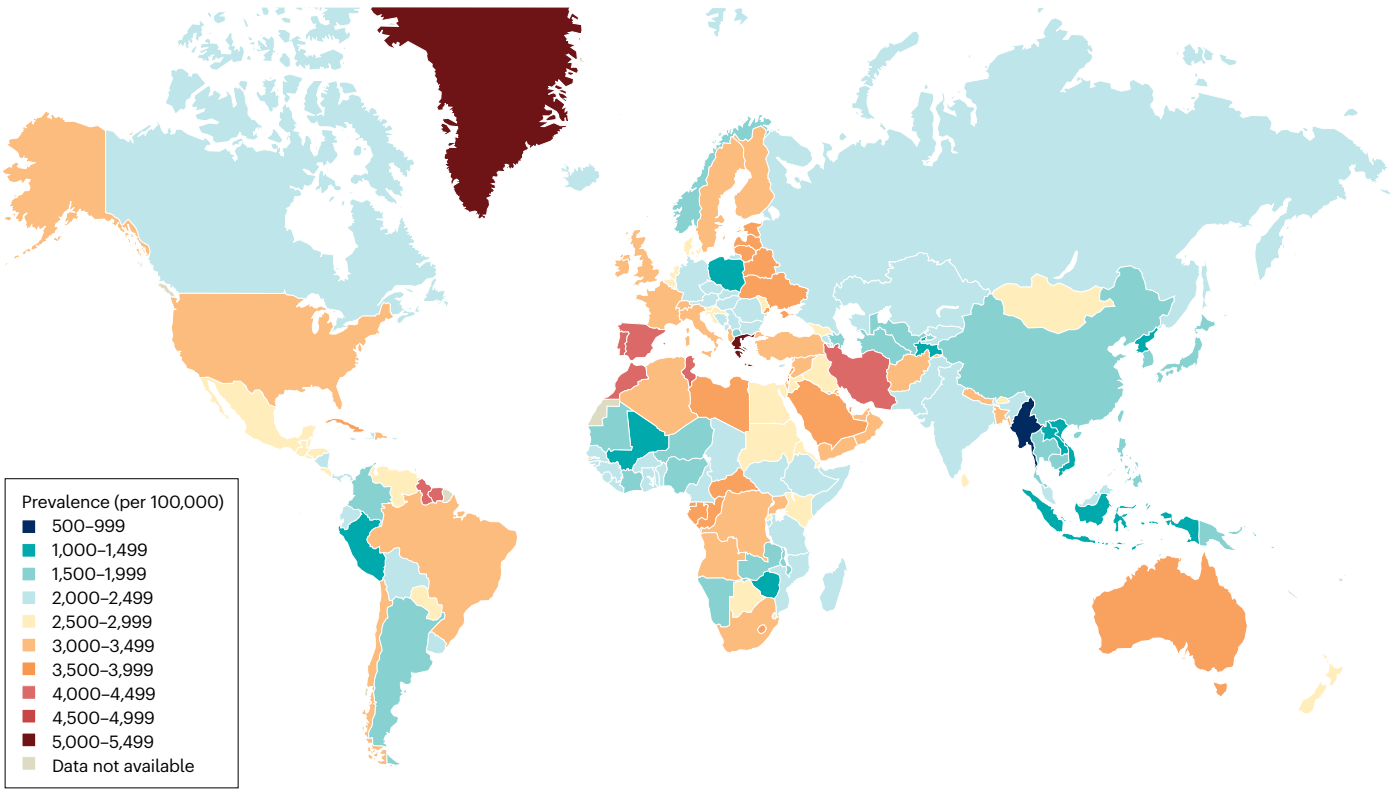

Fig. 2 | Prevalence of MDD by country. Prevalence of major depressive disorder (MDD) in 2019 per 100,000 individuals by country across all ages and for both sexes. Reprinted with permission from ref. 1, IHME.

factors are often at opposite ends of one dimension; for instance, childhood trauma (emotional and physical abuse or neglect) is a risk factor for MDD[52], whereas growing up in a supportive family environment is a strong protective factor for MDD[53]. In addition, neuroticism, introversion and rumination are other risk factors for MDD, whereas mastery, self-esteem and extraversion reduce MDD risk[54].

Some risk and protective factors directly affect the pathophysiological processes of MDD. However, it should be noted that the interpretation of these factors is not straightforward. These factors cannot only be considered 'environmental' as some also have a genetic influence (such as childhood trauma, low education and income) and shared genetic pleiotropy with MDD[55,56]. Moreover, many factors are bi-directionally associated with MDD. For instance, low socioeconomic status or lack of support contribute to MDD risk (social cause), but persons with MDD also have deteriorating social functioning that could result in smaller social networks, unemployment and lower income (social drift)[25]. In addition, many risk factors interact stochastically and non-linearly and can be proxies of other factors. For example, childhood trauma can negatively affect beliefs regarding interpersonal relationships and self-efficacy, which can affect other adaptive health and lifestyle behaviours (such as unhealthy patterns of sleep, physical activity, eating and alcohol consumption).

Neural pathways

A depressive episode is, at least in part, the net effect of disrupted network regulation involving multiple brain regions — rather than any individual brain region or neurotransmitter system — that interact to mediate various emotional, cognitive or somatic responses[25]. These patterns in the involved brain regions are highly variable, likely reflecting the substantial variability and heterogeneity in the clinical presentation of MDD itself (for example, differing severity, progression and symptom presentation).

Structural alterations. Convergent evidence has implicated the prefrontal cortex and anterior cingulate (regions involved in emotional, attention and cognitive control) in the pathology of MDD. Such evidence includes the substantial number of MDD-associated genetic variants that are found in genes expressed in these brain regions as well as reported increases in neuroinflammatory markers (for example, translocator protein density), reduced neurogenesis and grey matter volume in the prefrontal cortex and anterior cingulate of people with MDD compared with healthy controls. Moreover, hippocampal atrophy and thinner cortical grey matter have been found in several studies in the orbitofrontal cortex, anterior and posterior cingulate, and insula in persons with MDD, although effect sizes are small[57]. In line with this finding, individuals with MDD have subtle patterns of advanced age-related structural brain abnormalities[58] and subtle but extensive differences in white matter microstructure in multiple brain regions (particularly the corpus callosum and corona radiata), which may suggest structural disconnectivity[59]. Post-mortem studies of structural differences in MDD are limited. These studies have generally found smaller brain region volume, particularly the hippocampus, in

people with MDD compared with healthy controls[60,61]. Longitudinal analyses have also suggested subtle increases in hippocampal volume and cortical thickness in people with remitted MDD compared with non-remitted MDD[62,63].

Possible mechanisms responsible for these differences include abnormal axonal growth and abnormal dendritic growth and pruning, driven by, for example, alterations in the gut–brain axis, inflammation, dysregulation of the HPA axis, apoptosis and neurogenesis[64].

Of note, effect sizes for structural brain differences in MDD are small (effect sizes generally <0.2) and data from large analyses suggest that these differences have limited predictive value at the individual level[65,66]. Further, it remains unclear to what extent these differences should be interpreted as an aetiological risk factor, an early manifestation, a consequence of long exposure, and/or a scarring effect of illness-related processes or progression[67].

Functional alterations. Task-based and resting-state functional MRI studies have identified changes in the function of various brain regions and neural circuits in MDD[68,69]. Among the most well-studied regions are three major neural networks: the salience network, the frontoparietal network and the default mode network. Within the salience network, which is involved in detecting and assigning salience to emotional and motivational stimuli, people with MDD exhibit increased resting-state connectivity and heightened activation of the amygdala[70], dorsal anterior cingulate and anterior insula compared with healthy controls[25,40,64,71]. By contrast, within the frontoparietal network, which is involved in several higher-order cognitive processes, including the control of goal-directed behaviour, people with MDD demonstrate hypoconnectivity at rest and in response to negative stimuli (such as viewing pictures designed to elicit disgust)[72,73]. Studies have also reported both hypo- and hyper-connectivity within the default mode network in people with MDD[74,75]. This network of brain regions is involved in self-referential thinking, which may provide a neural explanation for the common presentation of rumination in MDD[68,69].

Neuroplasticity. Structural and functional brain differences in MDD also involve disrupted neuroplasticity and neurogenesis. Indeed, lower levels of the neurotrophin brain-derived neurotrophic factor (BDNF) have been found in sera and cerebrospinal fluid of people with MDD[76,77], although not always consistently. Moreover, some post-mortem studies[78,79] (but not all[80,81]) have found markers of neurogenesis, such as increased hippocampal volume, in people with MDD after receiving antidepressants compared with baseline or with people who were not receiving medication. Similarly, inhibiting neurogenesis in rodents using knockout models or chemical ablation seems to block the effects of antidepressants in some[82,83] but not all studies[84,85], with some indication that the variable results may be due to differences in chronic stressors, animal models and type of antidepressants studied[86,87]. In humans, pharmacological and other biological therapies, such as ECT and TMS, can normalize serum and plasma BDNF levels[82,88] and may be correlated with treatment response[82].

Dysregulated bodily stress systems

The pathophysiology of MDD extends beyond the central nervous system (CNS) and there is convincing evidence that MDD should be considered a whole-body condition. MDD is associated with chronic overactivity of the autonomic nervous system (with higher sympathetic tone among stress conditions), the immune system and the HPA axis (Fig. 3). Dysregulations of these systems are interconnected and often co-occur in MDD[89] and could contribute to the higher somatic comorbidity in MDD.

HPA axis. The HPA axis is a primary stress response system that enables adaptation to aversive physiological and psychological stimuli. The main components of the HPA axis are the paraventricular nucleus of the hypothalamus, the anterior lobe of the pituitary gland and the adrenal cortex. Dysfunction of the HPA axis can arise owing to genetic factors, early-life environment (including in utero environment) and current life stress[90]. For example, early-life stress (such as childhood maltreatment and abuse) has been shown to alter HPA axis function into adulthood[90].

One of the most studied and confirmed biological features of MDD is abnormal activity of the HPA axis. Corticotropin-releasing hormone is centrally involved in coordinating the neuroendocrine stress response. Data from post-mortem studies suggest hyperactivation of this pathway in relevant brain regions such as the paraventricular nucleus[91]. However, this is not corroborated by studies that measured corticotropin-releasing hormone in plasma and cerebrospinal fluid of people with MDD[91,92]. Further evidence of a role of the HPA axis in

Table 1 | Overview of risk and protective factors of MDD

Protective factors	Risk factors
Demographic determinants	
Male sex	Female sex
Older adult age	Adolescent and young adult age
High socioeconomic status	Low socioeconomic status
Psychological determinants	
Extravert personality profile	Neurotic and introvert personality profile
Internal locus of control, self-worth, mastery	Rumination and external locus of control
Good parenting	Childhood trauma and poor parental bonding
Sociocultural community determinants	
Economic security, social protection	Poverty, unemployment
Recent positive events (for example, holidays, promotion)	Recent negative life events (for example, divorce, loss)
Social support and equality	Lack of social support, bullying and discrimination, partner violence
Green spaces	War, natural disasters, air pollution, ambient noise
Neighbourhood security and safety	Unsafe neighbourhood, poor housing
Behavioural and health determinants	
Healthy lifestyle (physical activity, nutrient-dense diet, day–night structure)	Unhealthy lifestyle (physical inactivity, smoking, substance use, unhealthy diet)
Adequate treatment provision and adherence	No or poor treatment, treatment non-adherence
Good physical health	Somatic diseases, obesity and functional limitations
Good youth mental health	Early-onset anxiety or other mental disorders

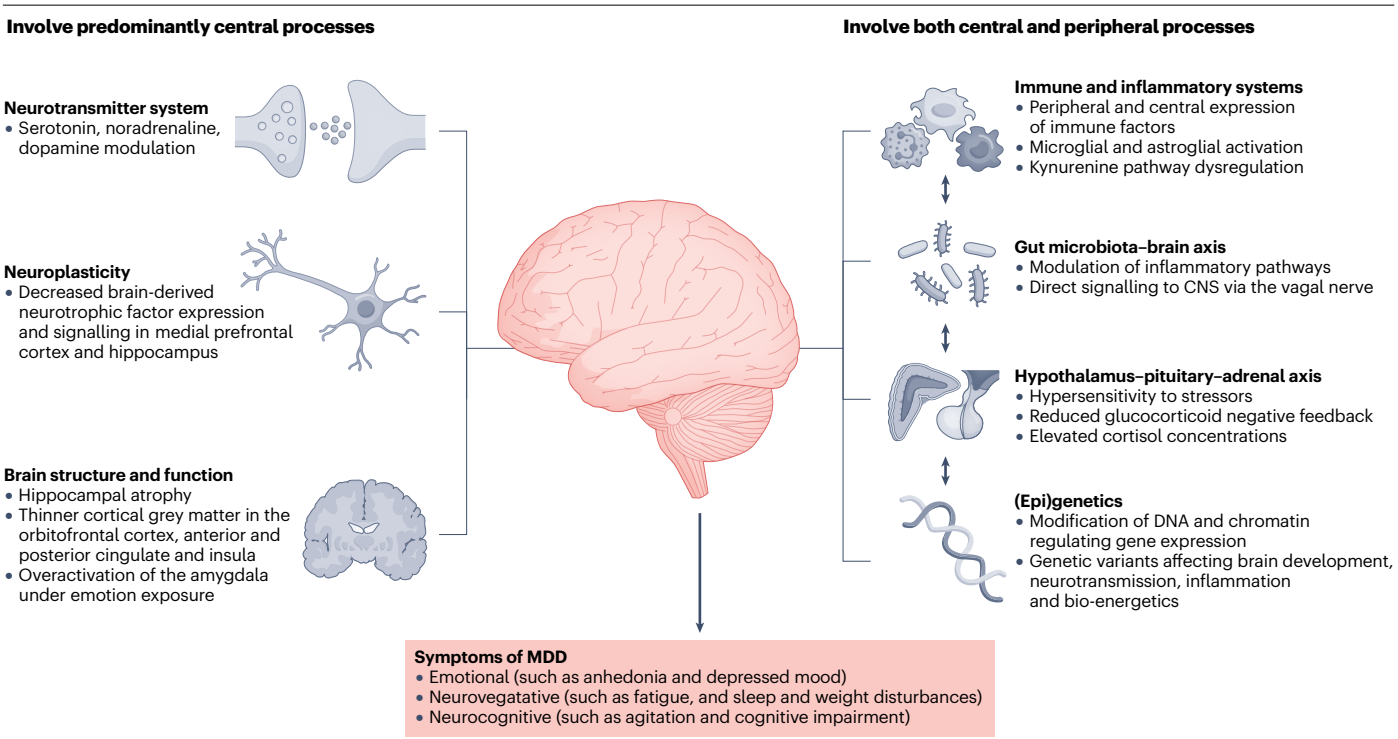

Fig. 3 | Biological mechanisms of action implicated in the pathogenesis of MDD. Diverse mechanisms have been implicated in the pathogenesis of major depressive disorder (MDD). Bidirectional arrows represent the likely interaction of these mechanisms. Other pathways that are not illustrated in this figure are also likely to be involved such as autonomic nervous system activity, metabolic differences and mitochondrial dysfunction. CNS, central nervous system.

MDD includes increased concentrations of the stress hormone cortisol in response to stressful stimuli (such as public speaking tasks and demanding cognitive tasks) compared with healthy controls, whereby both groups had similar cortisol levels at baseline and during a stressful stimulus but people with MDD exhibited a higher cortisol level during the recovery period[93]. Indeed, meta-analyses concluded that cortisol levels (measured in saliva, cerebrospinal fluid, urine or hair) are slightly higher in persons with MDD than in healthy controls[77,94]. This increase in cortisol is more strongly seen in those with melancholic and/or psychotic features[95]. High salivary cortisol levels in mornings can prospectively predict risk for MDD onset, suggesting cortisol could also act as a potential biomarker for MDD[96,97]. In line with this finding, large-scale registry data have illustrated that treatment with synthetic glucocorticoids is associated with an increased risk of suicide and MDD, even when controlling for underlying medical disorders[98].

Despite these findings, whether direct targeting of the HPA axis leads to improvement of MDD is unclear. Available antidepressants, such as monoamine oxidase inhibitors and SSRIs, can modulate cortisol levels; however, few studies have correlated reduced cortisol levels with improved treatment response[95]. Moreover, based on encouraging preclinical studies, several (mostly small-scaled) RCTs have evaluated glucocorticoid-lowering compounds in MDD, including metyrapone, the mineralocorticoid receptor agonist fludrocortisone or the glucocorticoid receptor antagonist mifepristone[99,100]. However, results from these trials were inconsistent[99,100]. Further studies are required to identify subgroups of patients who are more likely to respond to treatments targeting the HPA axis.

Inflammation. Several lines of converging evidence support a role for inflammation in MDD[10]. Large meta-analyses have shown increased serum and plasma levels of a range of inflammatory markers in people with MDD compared with healthy individuals[101]. Longitudinal studies have demonstrated that baseline elevations in markers of inflammation including C-reactive protein (CRP) and IL-6 can predict risk of MDD onset[102]. Furthermore, previous severe infection (such as sepsis) and diagnosis of autoimmune conditions (such as multiple sclerosis) are associated with increased risk of future MDD[103,104].

The effects of pro-inflammatory or anti-inflammatory therapies on depressive symptoms also support a role of inflammation in MDD. Pro-inflammatory medications (such as interferon-α) can induce depressive symptoms in otherwise healthy individuals, typically within the first 3 months of treatment[105], and are feasible human models of depression. Conversely, anti-inflammatory TNF antagonists, such as infliximab, can improve depressive symptoms in people with inflammatory disorders (such as Crohn's disease and ankylosing spondylitis)[106]. Moreover, a small RCT in people with treatment-resistant MDD, while showing no effect on the primary depression outcome, found that infliximab improved depressive symptoms in a subgroup of people with elevated CRP[107]. However, a subsequent study stratified for inflammation at baseline and did not find any benefit of infliximab in people with bipolar depression[108]. Other anti-inflammatory therapies, including NSAIDs, COX2 inhibitors, minocycline and statins, have been shown to reduce depressive symptoms in meta-analyses, although data are inconsistent[109–111]. Some antidepressants (such as SSRIs) may also lower inflammation[112], and ECT reduces some cytokines such as TNF (although not others such as IL-6)[113]. Conversely, baseline

elevated inflammatory markers, such as CRP and IL-6, may predict poor antidepressant treatment response[114].

Central markers of inflammation have been less frequently studied. A meta-analysis found increased translocator protein, a PET marker of central inflammation, in the anterior cingulate cortex and temporal cortex in people with MDD compared with controls[115]. Similarly, levels of IL-6, TNF and IL-8 are increased in cerebrospinal fluid from people with MDD compared with controls[115]. Post-mortem studies of people who took their own lives and people with MDD have demonstrated mixed evidence of central inflammation, with some studies finding changes in microglial or astrocyte-specific markers in several brain regions (including the prefrontal cortex and the anterior cingulate cortex) and decreased markers in the prefrontal cortex[115] . This central inflammation can interfere with a range of processes related to MDD, including monoamine synthesis, regional brain activity, redox biology, mitochondrial biogenesis and neurogenesis[10]. Peripheral inflammatory pathways can also affect central inflammation via a range of mechanisms, including via permeable regions of the blood–brain barrier[116], afferent signalling (such as via the vagus nerve) and cytokine transport systems[117].

Gut microbiota–brain axis

The bidirectional relationship between the gut microbiota and the CNS (the gut–brain axis) could be involved in MDD and other mental and somatic disorders[118]. Gut bacteria have been implicated in the modulation of inflammatory pathways (such as the inflammasome pathway)[119] and direct signalling to the CNS via the vagal nerve, pathways that are also related to MDD[120]. Furthermore, secondary metabolites derived from the gut microbiota, such as short-chain fatty acids (for example, butyrate), are also implicated in gut–brain signalling[121]. These may modulate neuroimmune, vagal and epigenetic systems, among others, as well as depressive behaviour in animal models[121,122].

Animal models that either lack or have alterations in their gut microbiota (such as germ-free mice or animals that have received antibiotics) can provide insight into the role of the gut microbiota in disease pathology[123]. These mice exhibit reduced depressive-like behaviours (such as decreased immobility time in the forced swimming test) compared with mice with an intact gut microbiota as well as altered activity within implicated pathways such as enhanced HPA axis reactivity, decreased BDNF expression and increased hippocampal serotonin concentrations[124–126]. Further evidence comes from reverse-translation models, whereby germ-free mice models that receive microbiota transplantation from humans with MDD demonstrate increased depressive-like behaviours[125,126].

Evidence of a role of the gut–brain axis from human studies is also increasing. People with MDD generally exhibit differences in gut microbiota composition (such as higher *Alistipes* and *Parabacteroides* and lower *Prevotella* and *Coprococcus*) compared with healthy controls[127]. These bacteria have been implicated in pathways relevant to MDD; for example, lower levels of *Coprococcus* bacteria may impair production of short-chain fatty acids, which may have antidepressant effects and alleviate psychosocial stress in mice[128]. However, differences in gut microbiota composition are not consistent across all studies, likely owing to the inter-individual heterogeneity in microbiota composition[129]. Microbiota-targeted interventions, such as probiotic and prebiotic supplementation, faecal microbial transplantation, or dietary manipulation, have also received nascent support as an intervention in MDD[130,131]. For example, recent meta-analyses of emerging RCTs suggest that probiotic supplementation may improve depressive symptoms, particularly in those with clinical diagnoses, but there are currently few studies that have investigated this[132].

Diagnosis, screening and prevention

Diagnostic criteria

The primary approach for the diagnosis of MDD uses operational diagnostic criteria in the DSM-5-TR and the ICD-11 (refs. 12,13) (Box 1).

The two systems are well harmonized and there is no strong empirical evidence in support of one system over the other. However, some differences remain between ICD-11 and DSM-5-TR such as the inclusion of 'hopelessness' as a symptom, with a cut-off of 5 out of 10 symptoms for diagnosis in ICD-11 (DSM-5-TR has a cut-off of 5 out of 9 criteria for diagnosis). Moreover, DSM-5-TR introduced the diagnostic entity 'persistent depressive disorder', which subsumes chronic major depression, recurrent major depression with incomplete inter-episode recovery and dysthymic disorder, whereas dysthymic disorder is maintained as an entity in ICD-11 (defined as chronic subthreshold depressive state that is separate from chronic depression or recurrent depression). Mixed anxiety depression (that is, the equal presence of symptoms of anxiety and depression that do not meet criteria for depressive or anxiety disorder) is also in the ICD-11 but is not included in the DSM-5-TR[133].

Individuals with suspected MDD are evaluated for the presence of MDD symptoms over the previous 2 weeks. A crucial component of this process is to ensure that symptoms are not explained by other psychiatric or medical disorders or medication adverse effects. Moreover, symptoms need to be more severe than typical feelings of sadness. Of note, symptoms related to grief and bereavement require special consideration. ICD-11 criteria permit diagnosis of MDD in bereaved individuals but with a higher threshold. The DSM-5-TR has introduced a new entry called 'prolonged grief disorder', which is characterized by clinically significant distress or impairment for >12 months after the death of someone close[12]. Although a differential diagnosis between MDD and prolonged grief disorder should be assessed, both disorders can be diagnosed using the DSM-5-TR if criteria for both are met.

Given the variability and heterogeneity of MDD, there have been ongoing efforts to further characterize MDD into subtypes. In the DSM-5-TR, this is achieved with specifiers (Box 1).

Validity of the current operational diagnostic criteria

Depressive symptoms lie on a continuum in the general population (Fig. 4). Many difficulties arise in the categorization of these symptoms into clinical versus subthreshold presentations. Some of the criteria for MDD have more differential diagnostic power than others such as depressed mood and anhedonia[134,135], but the lack of a clear gold standard for diagnosis of MDD confounds further clarification.

Subthreshold depressive states (that is, those that do not meet the diagnostic threshold for MDD) do not necessarily equate to perfect health and can be associated with clinically important dysfunction. Moreover, subthreshold symptoms are a risk factor for future MDD diagnosis, with an estimated 3.8–18.9% of individuals with subthreshold symptoms progressing to MDD within 1–3 years in some studies[136,137]. Similarly, treatment of subthreshold symptoms can provide meaningful improvement in depressive symptoms and QOL. For example, an individual participant data network meta-analysis of internet CBT (iCBT) demonstrated the general efficacy of guided iCBT even among those with subthreshold depression (with baseline Patient Health Questionnaire-9 (PHQ-9) scores between 5 and 9), although efficacy was greater with higher baseline PHQ-9 scores[138].

Box 1

DSM-5-TR and ICD-11 criteria for MDD

Summarized diagnostic criteria for major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision (DSM-5-TR)

An individual should have at least five of the following symptoms during the same 2-week period. These symptoms should be present almost every day and should represent a change from prior functioning. Moreover, these symptoms should cause clinically meaningful distress or impairment, must not be caused by a substance or another medical condition, must not be better explained by schizophrenia spectrum disorders, and the individual must not have had a manic or hypomanic episode.

- Depressed mood[a]
- Substantially reduced interest or pleasure in all, or almost all, activities[a]
- Considerable weight loss when not dieting, weight gain, or decrease or increase in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Reduced ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a specific suicide plan, or a suicide attempt

Specifiers of MDD in the DSM-5-TR are as follows:

- Severity
- Course
- With psychotic features
- With anxious distress
- With mixed features
- With melancholic features
- With atypical features
- With catatonia
- With peripartum onset
- With seasonal pattern

Summarized criteria for a depressive episode according to the International Classification of Diseases 11th Revision (ICD-11)

Essential criteria for a depressive episode according to ICD-11.

An individual must show at least five of the following symptoms (of which one must be from the affective cluster). These symptoms must occur for most of the day, almost every day for at least 2 weeks. Symptoms must result in meaningful impairment and must not be better accounted for by bereavement, another medical condition, or substance or medication use. Moreover, the individual must not meet criteria for mixed episode.

Affective cluster:

- Depressed mood[a]
- Markedly diminished interest or pleasure in activities[a]

Cognitive behavioural cluster:

- Reduced ability to concentrate and sustain attention to tasks, or marked indecisiveness
- Feelings of low self-worth or excessive and inappropriate guilt
- Hopelessness
- Recurrent thoughts of death, recurrent suicidal ideation (with or without a specific plan), or evidence of attempted suicide

Neurovegetative cluster:

- Significantly disrupted sleep or excessive sleep
- Significant change in appetite or significant weight change
- Psychomotor agitation or retardation
- Reduced energy, fatigue or marked tiredness

[a]The presence of at least one of the two symptoms is mandatory for diagnosis.

Proposed alternative diagnostic systems

Two alternative approaches to conceptualizing and studying psychopathology have also been proposed: the Research Domain Criteria (RDoC) by the US National Institute of Mental Health[139] and the Hierarchical Taxonomy of Psychopathology (HiTOP)[140,141]. These proposed systems aimed to address the limitations of the DSM-5-TR and ICD-11 such as boundary issues between the subthreshold and clinical presentations, the heterogeneity within a diagnostic category, and limited attention to aetiology[140]. Both systems focus on underlying mechanisms and processes that cut across multiple diagnostic categories (transdiagnostic) and frame mental disorders on a continuum rather than being binary categories (dimensional).

RDoC is more preclinical and research-oriented, focusing on key biobehavioural and aetiological mechanisms, whereas the Hierarchical Taxonomy of Psychopathology is derived from statistical modelling and is more data-driven and descriptive. Whether these systems can complement, supplement or replace the conventional DSM and ICD paradigms is unclear. RDoC has been criticized as having uncertain validity, not discriminating between 'normal' neurobehavioural elements or symptoms and pathology, and conflating different psychiatric disorders by similarities in cognitive, brain imaging, genetic or biomarker data without consideration for clinical and environmental context[142,143].

Screening

Screening can target all members of the general population (universal screening) or can focus on individuals at high risk (selective screening). The PHQ-9 is the most widely used screening tool for MDD as it is freely available, can be self-reported, rapidly scored by clinicians, and has been translated and validated in multiple languages and contexts[144]. Moreover, a meta-analysis of 29 studies reported that the PHQ-9 had a higher sensitivity than semi-structured interviews (sensitivity 0.88, specificity 0.85) with a cut-off of ≥10, which is typically used to indicate elevated depressive symptoms and possible MDD[145]. Other screening

tools include the Centre for Epidemiologic Studies Depression Scale (CES-D), General Health Questionnaire-12 (GHQ-12) and the WHO-Five Well-being Index (WHO-5)[146].

Despite the psychometric validity of screening tools, there is limited support for screening programmes on clinical outcomes. Only one RCT has evaluated the effect of screening programmes for MDD on the general community[147]. This study found a small but significant improvement in the mean score of reported depressive symptoms with a screening programme followed by structured interview and standard care compared with control (the education programme alone) at the 5-year follow-up (adjusted between-group difference of SMD −0.13, 95% CI −0.29 to 0.02).

The 2020 UK National Screening Committee does not recommend systematic universal screening for MDD in the general population owing to the lack of compelling evidence supporting reductions in severity, mortality or morbidity[148]. However, NICE guidelines recommend that clinicians are alert to possible indicators of MDD risk (such as previous history of MDD) and investigate this further in individuals with these indicators[149]. Similar guidance is provided by the 2013 Canadian Task Force on Preventive Health Care guidelines for screening within primary care, providing a weak recommendation against routine screening in this setting owing to limited data[150,151]. By contrast, the 2016 US Preventive Services Task Force recommends screening for depression in the general adult population on the condition that it be followed by accurate diagnosis, effective treatment and appropriate follow-up[152].

Prevention

Given its large burden[153], there is growing emphasis on the importance of prevention of MDD[25]. Preventive interventions could be multi-faceted, targeting the diverse social, economic, developmental, lifestyle, psychological and biological risk factors of MDD, and ranging from global, national, local, family and individual approaches. Grounded on a rights-based approach to mental health[154], societal efforts to alleviate poverty, inequity, loneliness, violence or bullying are called for[25]. Given that most of these risk factors are shared by most psychiatric as well as some non-communicable medical conditions, a shared framework for the prevention of non-communicable disorders is necessary[155].

Three types of prevention are used: universal prevention (targeting the whole population), selective prevention (targeting populations at high risk such as children of parents with depression or people who have undergone recent trauma) and indicated prevention (targeting people with subthreshold symptoms). Psychological interventions have been the most studied approach at the individual level, with one recent systematic review identifying 50 relevant trials (total $n = 14{,}665$)[156] that predominately examined CBT, interpersonal therapy, problem-solving and stepped care model interventions. Only one trial evaluated universal prevention, which comprised a teacher-led programme designed to teach cognitive restructuring and problem-solving skills in adolescents, with equivocal results[157]. However, selective and indicated prevention led to a 19% reduction (95% CI 9–28%) in the incidence of new episodes of depression within a year. However, longer-term trials are required to explore whether these effects persist[148]. School-based prevention programmes have also been investigated in numerous trials, with a meta-analysis of 81 unique studies reporting a small overall effect, with a larger effect in studies that targeted populations at risk[158]. Examples of such interventions include a behavioural and cognitive programme that resulted in lower rates of initial episodes of depressive disorders in an Icelandic cohort of 171 adolescents with subthreshold depressive symptoms over a 12-month period[159,160]. These results were replicated in a subsequent cohort of 168 Portuguese adolescents over a 24-month period[161].

Pharmacological prevention strategies targeting risk pathways have generally produced negative results, for example, targeting inflammation through the use of anti-inflammatory medications, such as aspirin and omega-3 fatty acids, and vitamin D insufficiency through vitamin D supplementation[162–164]. Moreover, despite cohort studies supporting a role for lifestyle factors and risk of MDD[165], few prevention intervention studies have targeted these factors[166,167].

Management

Four broad complementary treatment options are effective for MDD, namely psychotherapy, pharmacotherapy, lifestyle interventions such as exercise, and brain stimulation. Different guidelines make specific recommendations regarding first-line and second-line treatments for MDD and maintenance treatment across age groups and special populations[149,168,169]. In general, a combination of approaches can often yield greater efficacy than one treatment alone.

The severity of depressive symptoms has a substantial influence on the selection of treatment modalities. Lifestyle interventions and psychotherapy, alone or in combination, may be sufficient for mild MDD, whereas pharmacotherapy or ECT are recommended, in combination with lifestyle interventions and psychotherapy, for severe MDD[149,170]. Ultimately, treatment plans that consider predisposing, precipitating and perpetuating factors are a widely accepted strategy to personalize care and should guide the informed shared decision-making treatment

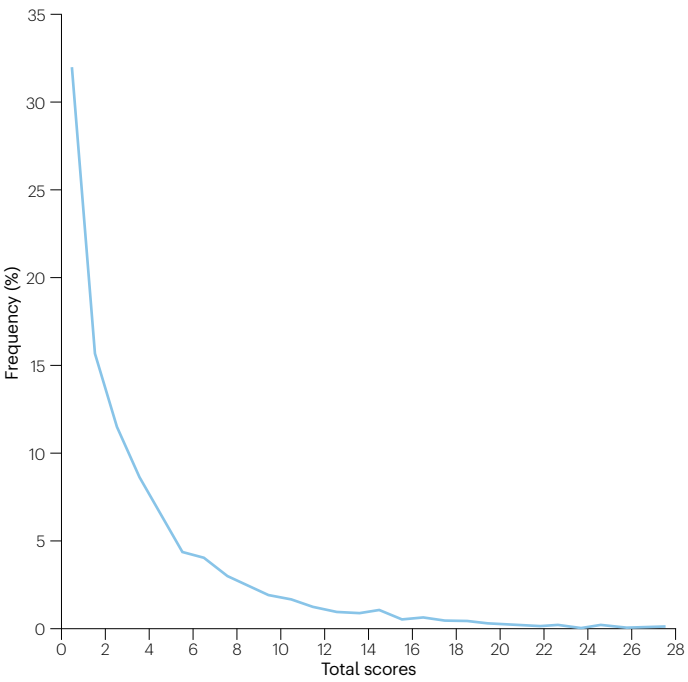

Fig. 4 | Total score distribution of the PHQ-9 in the general population. The distribution of Patient Health Questionnaire-9 (PHQ-9) scores across a nationally representative sample of 5,372 adult individuals in the United States[295]. A PHQ-9 score of ≥10 is generally considered as elevated depressive symptoms[145]. The data here are heavily right-skewed, with 31.9% reporting a score of zero, indicating that the general population report low to no depressive symptoms. Reprinted from ref. 295, Springer Nature Limited.

Table 2 | Stepped care for MDD

Levels of care	Indication and clinical actions[a]	Setting
1	All suspected presentations of depression and subthreshold depressive symptoms: diagnostic and risk assessment, psychoeducation on lifestyle factors (for example, diet, sleep, substance use, exercise), and psychological strategies (e.g. stress management, relaxation), active monitoring or watchful waiting	Self-care, general practitioner or community services
2	Mild to moderate depressive symptoms: psychotherapy, lifestyle approaches (for example, exercise), pharmacological treatment	General practitioner[b] or community services
3	Moderate depressive symptoms: psychotherapy, lifestyle approaches (for example, exercise), pharmacological treatment, transcranial magnetic stimulation and transcranial direct current stimulation can all be considered	Specialist service
4	Treatment-resistant depression and/or severe depressive symptoms; risk of harm to self or others; risk of physical impairment, psychotic symptoms: biological and non-biological treatment for treatment-resistant MDD (for example, electroconvulsive therapy), crisis services and inpatient care, until the level of care can be stepped down	Specialist service or inpatient care depending on circumstance

MDD, major depressive disorder. [a]Across all levels of stepped care, psychoeducation and interventions targeting lifestyle factors associated with MDD should always be considered[15,170]. The choice between treatments should be made in an informed and shared decision-making process with the individual, and based on experience with and availability of treatments among the health-care providers/services. [b]Referral from primary care actors to secondary or tertiary services is indicated based on clinical experience, severe presentation, or in the case of poor response to initial treatment. Data from NICE and RANZCP guidelines[149,170].

selection process[171,172] in a stepped care approach (Table 2). Considerations include past and family history of response to previous treatments, comorbidity, resources, skills and preference of an individual, and treatment availability. Moreover, the strength of evidence in support of a particular treatment should be considered during treatment planning. These considerations are of particular relevance to specific subpopulations such as in older adults in whom some risk factors are more prevalent, including loneliness, functional impairment and frailty, or multiple prescribed medications[173].

The therapeutic alliance and adherence to all treatments for MDD should be actively promoted. The clinician should establish a solid therapeutic alliance, understanding the worldview and conceptualization of distress of the person they are treating; collect social, pharmacological and medical history; measure depressive symptoms with validated tools; monitor adverse events; and facilitate multidisciplinary approaches and access to care for follow-up visits. Moreover, the inclusion of family, friends and carers, where possible and appropriate, in core decisions about the assessment, treatment and care of an individual may aid in adherence and provide complimentary support[15]. Similarly, peer support workers, generally employed by some health-care settings due to their lived experience of a mental health condition, may aid recovery by sharing coping strategies and advocating for the individual as well as by providing validation and reducing stigma[174].

Global access to care

The treatment gap – the percentage of individuals with mental disorders who have no access to treatment – is estimated at approximately 35–50% in HICs and 85% in low-income and middle-income countries (LMICs)[175]. Moreover, similar disparities have been reported between HICs and LMICs in obtaining treatment and treatment adequacy in people with MDD[176]. Several reasons have been proposed for this disparity, including a substantial difference in the availability of mental health workers between HICs and LMICs. The WHO Mental Health Atlas estimates that there are <1.4 mental health workers per 100,000 population in LICs compared with >62 workers per 100,000 population in HICs[177]. Similar disparities are also seen in the difference in provision of treatment, whereby 71% of HICs report pharmacological and psychosocial interventions being available in >75% of primary care centres compared to 13% of LMICs[177]. Moreover, there are also stark disparities in government financial funding for mental health care (LMICs: US$ 0.37 versus HICs: US$ 52.73 per capita)[177].

The WHO Mental Health Gap Action Programme Intervention Guide (mhGAP-IG) is an example of an initiative aiming to address this treatment gap by improving access to mental health services, particularly in LMICs[178]. Although specialized mental health-care facilities and clinicians are relatively scarce in LMICs, alternative approaches to mental health care using existing infrastructure (such as community halls and churches) and available workforce (such as peers, clergy and traditional healers) have shown efficacy in LMIC settings[179].

Psychotherapy

Available types of psychotherapy. In adults, psychotherapy is effective as a first-line treatment for MDD, particularly in those with mild to moderate MDD, used alone or in combination with pharmacological treatment[180,181]. Many different types of psychotherapies are effective, namely behavioural activation therapy, CBT, interpersonal psychotherapy, life-review therapy and third-wave psychotherapies[182].

CBT aims to identify negative thought patterns and replace them with positive and more realistic thoughts. 'Third-wave' CBT focuses on the process of thoughts rather than their content, emphasizing metacognition, acceptance and mindfulness. Several therapies are encompassed by third-wave CBT, including acceptance and commitment therapy, dialectical behaviour therapy, metacognitive therapy, and mindfulness-based interventions. Behavioural activation therapy is often incorporated into CBT-based therapies and seeks to increase engagement in fulfilling activities while reducing involvement in those that worsen depressive symptoms. Components of behavioural activation therapy include activity monitoring, goal assessment, scheduling, skills training, relaxation techniques, contingency management, verbal behaviour targeting and avoidance addressing.

By contrast, psychodynamic therapy is rooted in traditional psychoanalysis and targets unconscious processes and patterns contributing to current issues, promoting self-awareness and change. Problem-solving therapy provides a structured framework of psychoeducation and interactive exercises that aims to help individuals identify and overcome stressors and make effective decisions. Moreover, interpersonal therapy helps individuals enhance communication and resolve problems in relationships with an aim to address the related emotional distress and improve overall functioning. Lastly, non-directive supportive counselling provides unstructured therapy, driven by the individual, focusing on active listening and support rather than specific techniques or advice.

Efficacy. A network meta-analysis of several psychotherapies found that most modalities were more effective than care-as-usual and waitlist controls; however, non-directive supportive counselling and psychodynamic therapy did not differentiate from pill placebo[182]. Problem-solving therapy had the most enduring effects and demonstrated a greater effect than the other interventions at 12 months of follow-up[182]. Owing to the similar efficacy of most psychotherapies, the treatment approach for individual patients should be guided by clinical formulation, clinician training and experience, and the preferences and presentation of the individual with MDD.

Online and remote psychotherapy, such as iCBT, is available via online apps and platforms[183]. These modalities permit access to care when in-person psychotherapy is unavailable due to cost and/or access barriers. iCBT comprises a heterogeneous set of components together with the core CBT principles[183]. Meta-analyses comparing iCBT with face-to-face CBT have suggested comparable efficacy between these two modalities across a range of psychiatric disorders[184]. However, high dropout rates in trials of iCBT and low time on iCBT websites have been reported, particularly for self-guided interventions[185]. Hybrid models with human contact, in addition to automated encouragement can promote adherence to iCBT[183].

Pharmacological treatment

Nomenclature. Classically, most commonly used psychopharmacological agents have been divided mainly into antidepressants and second-generation antipsychotics. Antidepressants can also be divided into mechanism-informed categories, including tricyclic antidepressants (TCAs), SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline and dopamine reuptake inhibitors, noradrenaline and specific serotonergic antidepressants, and noradrenaline reuptake inhibitors. Similarly, second-generation antipsychotics can be divided based on their mechanisms (typically antagonism, agonism or partial agonism at monoaminergic receptors).

The Neuroscience-based Nomenclature project has introduced a scientifically and clinically informative nomenclature for psychopharmacological agents, which is based on the pharmacological target of antidepressants (such as serotonin or dopamine), their mode of action (such as reuptake inhibition or partial agonism), approved indications, and further clinical insights[186,187]. However, the mechanisms of pharmacological treatments are likely complex and involve multiple pathways such as hippocampal neurogenesis and targeting inflammation. As such, categorizations based primarily on monoamine receptor modulation should not be seen to explain the full therapeutic effect.

Efficacy. Clinical improvement with most antidepressants is expected in the first six weeks from the initial dose with a regular titration schedule[188]. Guidelines such as those developed by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and NICE[149,169] generally recommend the continuation of pharmacotherapy for 6–9 months after achieving remission, with regular review. In adults, almost all antidepressants may have similar effectiveness[189,190] (Fig. 5). Agomelatine,

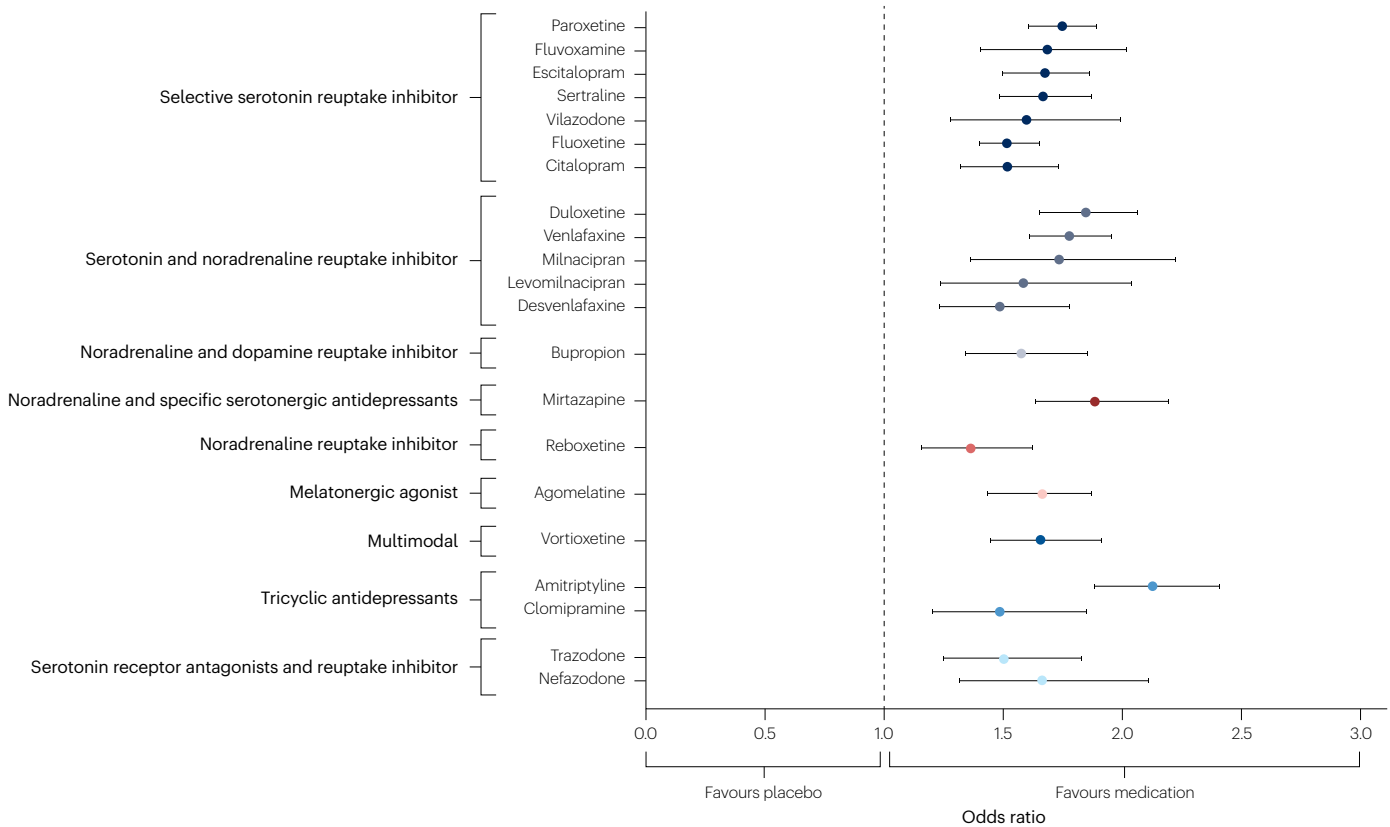

Fig. 5 | Efficacy of different antidepressant medications compared to placebo in MDD. Data from a large network meta-analysis (522 trials, $n = 116{,}477$) of 21 antidepressant medications for major depressive disorder (MDD)[191]. The effect sizes for individual medications that are used to treat MDD are variable; however, all evaluated antidepressants had greater effect in reducing depressive symptoms compared with placebo, with most medications reporting a moderate effect size[191]. Adapted from ref. 191, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Box 2

MDD in children and adolescents

The prevalence of major depressive disorder (MDD) in children is low (<1%) globally and without substantial sex differences[1]. However, prevalence rises during adolescence (2.14% at 15–19 years old) with a higher prevalence in women, similar to what is observed in adulthood[1].

Diagnosis of MDD in children and adolescents largely follows the same criteria as in adults. However, as children and adolescents may not be able to express their symptoms adequately, diagnosis may require additional assessment measures. Specific screening tools, such as the Beck Depression Inventory and Patient Health Questionnaire for Adolescents, are commonly used tools and have a high sensitivity in this population[296]. Furthermore, manifestations can present differently within this age group than in adults, such as manifesting as irritability rather than as depressed mood. Otherwise unexplained behaviour changes, such as declining academic performance, may be an indicator of concentration and attention symptoms of depression. Differential diagnosis with other psychiatric disorders, such as attention-deficit/hyperactivity disorder, is also required given the overlapping symptom presentation.

Children and adolescents have poorer responses to pharmacological therapies for MDD than adults, which may be driven by higher placebo response rates in younger people[193]. However, fluoxetine alone or in combination with cognitive behavioural therapy is more effective than placebo in children and adolescents[193,194]. Interpersonal psychotherapy, problem-solving, family therapy and psychodynamic-oriented psychotherapies all have supporting evidence as effective psychotherapy options with the strongest evidence for interpersonal therapy[193,194]. NICE guidelines recommend the use of fluoxetine only in combination with concurrent psychological therapy, whereas other guidelines, such as those from the American Academy of Child and Adolescent Psychiatry, recommend fluoxetine monotherapy in combination with cognitive behavioural therapy[297,298].

Around 30%–40% of children with MDD do not adequately respond to first-line interventions[299]. The evidence base for the management of treatment resistance in children and adolescents is limited; however, general strategies include changing medications (such as to a different serotonin reuptake inhibitor), pharmacological or psychotherapy augmentation strategies (such as adding cognitive behavioural therapy or an additional medication, or dose escalation), and introducing additional treatment modalities (such as transcranial magnetic stimulation)[299].

amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine have higher efficacy than other antidepressants; however, although the effect sizes of fluoxetine, fluvoxamine, reboxetine and trazodone might be lower, these differences could reflect variations in methodology, era of study and population as much as they reflect the treatments[191,192]. In children and adolescents with MDD, fluoxetine is the only antidepressant with supporting evidence, and has been shown to decrease depressive symptoms, and increase the odds of response and remission[193,194] (Box 2).

Second-generation antipsychotics can be used to augment antidepressants in people who do not respond to initial pharmacological treatment. In adults, low doses of aripiprazole and risperidone might be initially preferred to augment antidepressant treatment, although olanzapine, quetiapine and brexpiprazole can also be considered[195]. Augmentation with aripiprazole has been demonstrated to be superior to placebo augmentation[196] as well as superior to switching to bupropion in older adults with treatment-resistant depression[197].

Evaluating treatment response. A reliable biomarker for treatment response in depression (or psychiatry more broadly) is not available although clinical, blood, genetic and neuroimaging approaches are under study[198,199]. For example, pharmacogenomic-guided treatment refers to an approach whereby medications are selected based on the genetic variation of an individual related to drug metabolism, response and adverse reactions. Several RCTs have investigated the efficacy of this approach in MDD, with some studies reporting improved response[200,201]. However, the largest (n = 1,944) study found only a small, non-persistent effect on symptom remission in those who received pharmacogenetic-guided treatment compared with usual care at follow-up[202]. Other studies have also reported negative findings[203]. Further trials are needed to further elucidate the validity of biomarkers for treatment response in depression. Until these approaches can be used in clinical practice, the choice of the first-line pharmacological treatment should be guided by other clinical factors such as clinical profiles and clinical formulation, individual preferences, past response patterns, tolerability and safety.

Tolerability, safety and discontinuation. Antidepressants have a range of tolerability issues that can affect treatment adherence (Table 3). Adverse effects differ between the type and class of antidepressant medication. TCAs typically have a low therapeutic index (the ratio of lethal dose to therapeutic dose), which raises safety considerations that require clinical monitoring for symptoms of toxicity (such as tremors, confusion and muscle rigidity)[204]. More recent antidepressants (such as SSRIs and SNRIs) are more tolerable although patients can still have adverse effects, including diarrhoea, nausea, sweating and sexual dysfunction with SSRIs, increased blood pressure with SNRIs, or nausea with vortioxetine[205]. Monoamine oxidase inhibitors, such as phenelzine and tranylcypromine, can cause hypotension and require dietary restriction to mitigate food–drug interactions.

In general, the tolerability of antidepressants is similar in adolescents and adults. However, most agents are less well tolerated in elderly individuals and, therefore, generally good psychopharmacological practice principles apply in these individuals, namely preferring slow titration and safer medications with fewer drug–drug interactions[206].

Several adverse health outcomes have been reported with antidepressants in the general clinical population, particularly in pregnant women. However, this evidence is affected by several sources of bias, including confounding due to not controlling for an underlying psychiatric condition[207]. According to established quantitative criteria, there is no convincing evidence of any long-term untoward health outcome associated with the use of antidepressants in people with MDD[207].

A report by the USA National Health and Nutrition Examination Survey found that 13.6% of people who used antidepressants had received this therapy for >10 years[208]. Ongoing prescription of antidepressants should be routinely re-evaluated to prevent relapse, which is more frequent after discontinuation of antidepressants[209], to ensure the medication is still effective, and that the benefit of treatment outweighs potential adverse effects. If discontinuation is warranted, patients should be monitored for symptoms that are associated with abrupt cessation such as nausea, flu-like symptoms and insomnia[210]. NICE guidelines recommend gradual dose reduction (also known as tapering) and monitoring and management of withdrawal symptoms throughout this process[149].

Brain stimulation

Several brain stimulation techniques are effective for the treatment of MDD[211]. Some techniques are indicated only for treatment-resistant depression and are described in the dedicated section below.

The most widely used and studied neurostimulation therapy is ECT, which encompasses the induction of seizures by applying unilateral or bilateral electrodes on the temporal region of the head while patients are under general anaesthesia. The main adverse effect is anterograde and retrograde amnesia, which is generally transient and typically resolves within 2–4 weeks[212]. Response to treatment occurs rapidly, with one RCT reporting an initial first response by the end of the first week of ECT in 54% of participants[213]. ECT is recommended for severe depression, particularly in those with immediate suicide risk and in those with psychotic and catatonic symptoms and in those with treatment-resistant depression[170,212]. Indeed, ECT is most widely used in individuals with treatment-resistant MDD, in whom pooled remission rates of 52.3% and pooled response rates of 74.2% have been documented[214]. Similar rates have been reported in older adults, although some studies indicate that older adults may be more likely to respond to ECT than younger populations[215]. In a meta-analysis, ECT was significantly more effective than placebo or pharmacotherapy for the treatment of severe depression[216]. Moreover, ECT is more effective than TMS, especially for psychotic depression[217]. ECT also seems to be either superior or comparable to ketamine in reducing depressive outcomes in people with MDD, although this observation is based on a limited number of studies[218,219].

Table 3 | Characteristics of most frequently used antidepressant pharmacotherapy for MDD

Medication class	Examples	Proposed mechanisms of action[a]	Common adverse effects[b]	Clinical notes
Selective serotonin reuptake inhibitors	Fluoxetine, citalopram, escitalopram, sertraline, fluvoxamine, vilazodone	Serotonin reuptake inhibitor	Sexual dysfunction, nausea, insomnia	Most frequently prescribed class of antidepressants
Serotonin and noradrenaline reuptake inhibitors	Venlafaxine, duloxetine, levomilnacipran, desvenlafaxine	Serotonin, noradrenaline reuptake inhibitor	Dizziness, sexual dysfunction, nervousness	May also improve musculoskeletal, central and/or neuropathic pain
Noradrenaline and dopamine reuptake inhibitors	Bupropion	Reuptake inhibitor and releaser of noradrenaline and dopamine	Nervous system disorders (for example, agitation, anxiety), headache, gastrointestinal disorders (for example, gas, constipation)	Low likelihood of sexual dysfunction, also targets smoking
Noradrenaline and specific serotonergic antidepressants	Mirtazapine	Noradrenaline, serotonin receptors antagonist, antagonist at histamine, alpha receptors	Somnolence, dry mouth, increased appetite	May improve sleep when administered at night, can improve appetite
Noradrenaline reuptake inhibitors	Reboxetine	Noradrenaline reuptake inhibition	Drowsiness, gastrointestinal disorders, insomnia	Low likelihood of sexual dysfunction
Melatonergic agonist	Agomelatine	Melatonin receptor agonist, serotonin receptor agonist and antagonist	Eczema, paraesthesia, pruritus	May improve sleep when administered at night
Multimodal	Vortioxetine	Serotonin reuptake inhibitor, serotonin receptors partial agonist and antagonist	Nausea, diarrhoea, dizziness	May improve cognitive function
Tricyclic antidepressants	Clomipramine and amitriptyline	Noradrenaline, serotonin reuptake inhibitor, serotonin receptor antagonist, antagonist at histamine, cholinergic and alpha receptors	Dry mouth, somnolence, dizziness	Effective for melancholic depression, low toxicity index, for treatment-resistant MDD
Second-generation antipsychotics	Olanzapine	Dopamine partial agonist	Somnolence, headache, increased appetite	Metabolic adverse events should be monitored
Monoamine oxidase inhibitors	Tranylcypromine and phenelzine	Inhibition of enzymatic breakdown of dopamine, noradrenaline, serotonin	Nausea, pain, skin reaction at the patch site (if transdermal application)	Available transdermally, risk of serotonin syndrome with tyramine food and other medications
NMDA receptor modulator	Ketamine	Glutamate NMDA receptor antagonist	Nausea, dizziness, dissociation	Quick action, for treatment-resistant MDD, risk of abuse

MDD, major depressive disorder; NMDA, *N*-methyl-D-aspartate. [a]Mechanisms are based on the Neuroscience-based Nomenclature[186,187]; however, there are likely additional mechanisms involved. [b]Adverse effects are based on the three top-ranked side effects reported in the Side Effect Resource (SIDER) database; however, there is substantial variability in adverse effects between individuals[205].

Other stimulation techniques for MDD are TMS and transcranial direct current stimulation[211]. With TMS, a magnetic field generates a current that stimulates proximal brain areas. Different forms of TMS exist, some of which require shorter treatment sessions (such as theta burst TMS). One example of such forms is the Stanford Neuromodulation Therapy protocol, which requires a reduced duration to prior TMS methods and has demonstrated a 52.5% reduction in reported average depressive symptoms from baseline in the active treatment group compared with 11.1% of participants receiving a sham treatment[220]. By contrast, transcranial direct current stimulation (TdCS) involves the application of direct current to specific areas of the scalp, which modulates neuronal activity in targeted brain regions. The efficacy of TMS and TdCS are mediated by common downstream mechanisms, including gene transcription modulation and de novo protein expression, structural brain changes, and complex firing and network properties[221]. TMS and TdCS have similar effect sizes, are safe and acceptable, and the choice between the two should be based on clinician experience with the two modalities, availability and preference of the person with MDD[211].

Exercise and other lifestyle interventions

Large meta-analyses support the use of exercise interventions in improving depressive symptoms[222,223]. Aerobic exercise or resistance training are the most well-supported forms of exercise, and guidelines recommend at least 2–3 weekly sessions, each of 45–60 min in duration with moderate intensity[15]. Exercise should ideally be supervised, in groups and tailored to individual preferences, which should also promote adherence[224].

Interventions that address other lifestyle factors have emerging support for use in MDD. The strongest evidence for individual lifestyle interventions for the treatment of MDD is for exercise, relaxation, and work-directed (such as return-to-work initiatives, workplace and role modifications), sleep and mindfulness-based interventions[15]. In addition, weaker evidence supports the use of interventions aimed at improving diet quality, increasing exposure to green spaces, smoking cessation, reducing loneliness or improving social support to reduce depressive symptoms in people with MDD[15]. In addition to potential benefits on depressive symptoms, lifestyle interventions are likely to be beneficial in addressing the high level of physical comorbidity present in people with MDD by improving metabolic health and cardiorespiratory fitness[225].

Combined approaches

A combined treatment approach can be useful for patients with MDD. Combined pharmacological and psychological treatments for MDD outperform psychological or pharmacological treatment alone[226,227] for both acute treatment, relapse prevention, and adherence to treatment[181]. Psychotherapy is also indicated to prevent relapse when tapering an antidepressant, providing an effect that is comparable to continuing the pharmacological treatment[228]. Across all levels of stepped care, psychoeducation and interventions targeting lifestyle factors associated with MDD should always be considered[15,170].

Treatment-resistant MDD

More than two-thirds of people with MDD do not achieve remission after first-line pharmacological treatment, and 15–30% of patients do not respond to two or more medications[229]. Treatment-resistant depression is defined as <25–50% improvement of depressive symptom severity, after at least two pharmacological treatments, at appropriate doses, for at least 4–6 weeks each[230]. Earlier age of onset of the first depressive episode and elevated suicidality are associated with treatment-resistant MDD[231]. Treatment resistance should not solely be attributed to MDD itself, and other causes of treatment failure should also be considered such as psychiatric comorbidity (for example, comorbid anxiety disorders)[231], misdiagnosis and patient factors (for example, poor treatment adherence, job satisfaction, personality disorders)[35,229]. Furthermore, MDD is often inadequately treated and under-recognized in populations with comorbidities and/or older adults, which can likely contribute to poor treatment response[173]. For example, one study in people >70 years of age found that 43–69% of individuals with depression did not receive treatment over an 18-month study period[232].

The first step in patients with suspected treatment-resistant MDD is clinical review, confirming diagnosis and exploring confounders such as comorbidity and substance use. In addition to offering evidence-based treatments for treatment-resistant MDD, clinicians should identify modifiable factors that could be contributing to persistent depressive symptoms[229]. Management of treatment-resistant depression should be based on treatment availability, history of previous responses, safety and individual preference. An initial decision to be made after non-response to pharmacological intervention is whether to increase the dose of current antidepressant medications, switch antidepressant medications, combine with additional antidepressant medications, or augment treatment with additional medications such as atypical antipsychotics (aripiprazole, brexpiprazole, quetiapine, olanzapine or risperidone), dopamine compounds (modafinil or lisdexamfetamine) or lithium[233].

In 2019, esketamine (a nasal spray) received regulatory approval for treatment-resistant MDD. Existing studies have demonstrated the efficacy of this therapy[234,235]; however, concerns have been raised regarding the design of the initial studies, the reported magnitude of effect, long-term safety and their applicability to older adults[236]. Intravenous ketamine can also be used for short-term treatment of treatment-resistant MDD[237]. Of note, patients should be monitored for the development of dissociative symptoms for at least 1 h post-infusion after administration of esketamine and ketamine[238].

Other therapies for treatment-resistant MDD include ECT and neurostimulation. The use of unilateral or bilateral ECT for treatment-resistant MDD is well supported and has a long history of use[212]. TMS and TdCS are also effective for the management of treatment-resistant depression[239,240]. Vagus nerve stimulation can be considered after other treatments for treatment-resistant MDD have been trialled[241]. Vagus nerve stimulation uses an implantable device with intermittent electrical stimulation of the left cervical vagus nerve. Deep brain stimulation is being evaluated for the management of treatment-resistant MDD, although there are methodological and procedural uncertainties regarding the optimal brain area to target and supporting evidence is limited[242].

Pregnancy and post-partum

Pregnant women with MDD should be offered psychotherapy as a first-line treatment. Safe physical activity and exercise should also be suggested[243]. Use of antidepressants is not contraindicated in pregnant women[207,244], and previous clinical history should inform treatment choices. Brexanolone, a novel positive allosteric modulator of γ-aminobutyric acid type A (GABAA) receptors, may be fast acting and is effective in treating post-partum depression[245].

Quality of life

Several tools are available to assess QOL within psychiatry, for example, the widely used World Health Organization Quality of Life Instrument-Short Version (WHOQOL-BREF) and the 36-item Short-Form Health Survey (SF-36)[246]. MDD is associated with substantial decrements in QOL across multiple domains, including physical, mental and social QOL[247]. Notable factors affecting QOL in people with MDD are the physical components of MDD itself, the high prevalence of medical and psychiatric comorbidities in people with MDD, stigma[2], and impairments in financial[4], relationship[5,6] and educational[3] functioning.

In addition to the mood alterations that are characteristic of MDD, other highly prevalent symptoms can impair QOL in these patients. For example, sleep disturbances, such as insomnia, occur in 80–90% of people with MDD, are associated with reduced QOL[248], and are independently associated with suicidal ideation and suicide attempts[249]. Moreover, cognitive symptoms occur in up to 94% of people experiencing a depressive episode and are associated with reduced QOL[250,251]. Indeed, executive function, memory and attention are subtly impaired in people with MDD compared with healthy controls[252] and can persist after MDD remission in 39–44% of people[250,252]. Some antidepressant medications, particularly vortioxetine, may mitigate cognitive impairment[253].

MDD is also associated with a substantial increase in morbidity and mortality[254] and can result in higher levels of disability and impairment than most physical conditions, even cardiovascular diseases and cancers[255]. Observational studies and emerging Mendelian randomization studies have found that MDD increases future risk of several physical disorders, including cardiovascular disease, metabolic syndrome, obesity, cancer and type 2 diabetes mellitus. These associations are often bidirectional, with somatic disorders also increasing the risk of future MDD. Moreover, a large umbrella review found that MDD was associated with increased all-cause or cardiovascular-related mortality in several populations[256]. MDD is also associated with other types of comorbid mental disorders, including anxiety disorders[257], as well as alcohol use disorder and other substance use disorders[258].

Despite growing efforts to increase awareness of mental illness and to reduce negative attitudes towards people with MDD and treatment, public stigma towards people with MDD is a persistent global issue[259]. This stigma, coupled with internalized negative beliefs by individuals with mental disorders (self-stigma), are associated with adverse effects on treatment seeking and adherence, QOL, and suicidal behaviour[260].

MDD is also associated with adverse functional outcomes through effects on education, vocation and economic status, and relationships. MDD during childhood, adolescence and young adulthood is associated with poorer academic performance, in addition to premature termination and reduced odds of engaging in secondary and tertiary education[3,261,262]. Moreover, MDD is associated with higher levels of school absenteeism and truancy[263].

In adulthood, MDD is also associated with poorer economic outcomes such as household income and days out of role[264,265]. For example, a recent observational study using data from the UK Biobank found that MDD was associated with several adverse employment outcomes, including higher odds of sickness or disability, unemployment, early retirement, reduced weekly hours worked, and lower household income, which was partially supported by a Mendelian randomization analysis[4]. Although the financial costs of MDD are difficult to quantify on a global scale, studies across Europe, North America and Asia have all found that the substantial economic burden of MDD is primarily driven by indirect costs (such as work absenteeism and comorbidities) and seems to be increasing over time[266,267].

MDD is also associated with parental and marital dysfunction. Current MDD or more severe depressive symptoms are associated with negative parenting behaviours (such as higher levels of hostile behaviour, lower levels of engagement and positive social interactions) in both mothers[268] and fathers[5]. Mental disorders have also been associated higher risk of future divorce[6] and higher levels of marital discord[269].

Outlook

Emerging interventions

Several interventions are being developed for MDD[270,271]. In addition to pharmacological agents related to the re-allocation of atypical or novel molecules primarily acting on monoamine reuptake[270,271], mechanisms with promising data from phase II and phase III trials include acetylcholine inhibition, oestrogen and progesterone receptor agonism[272], GABA receptor positive allosteric modulation[273], and/or peroxisome proliferator-activated receptor-γ agonism[274]. Several nutraceutical compounds are being investigated with varying levels of evidentiary support[275]. Deployable and portable non-invasive brain stimulation is also under study, with research focusing on feasibility and methodological challenges[276].

Other approaches include medication repurposing. Several off-label interventions have emerging research for use in MDD, including antibiotics (such as minocycline)[277], insulin sensitizers (such as metformin)[278], and anti-inflammatory and lipidaemic agents (such as statins)[279]. Such off-label use of these therapies for MDD was largely initiated through clinical observation in other cohorts or through the elucidation of shared biological mechanisms[280]. A new generation of studies is using stem cells and other discovery platforms to identify candidate molecules for repurposing[281,282].

The recent resurgence in psychiatric research on the use of serotonergic (such as LSD and psilocybin) and atypical (such as MDMA) psychedelic agents has garnered large general interest as potential interventions for MDD and other mental disorders[283]. Although few RCTs have been conducted and many of the early studies were beset with methodological problems, recent meta-analyses have estimated a moderate to large effect size in improving depressive symptoms and negative mood states[284]. However, due to the euphorigenic and dissociative properties of psychedelic agents, concerns regarding effective blinding and driving expectancy require further attention in future studies as do safety concerns and long-term outcomes. Moreover, repurposed recreational drugs all have an established risk of abuse and well-described adverse event profiles; the extent to which these properties will limit the use of these drugs beyond clinical trials remains uncertain.

Addressing the mental health treatment gap

Another factor that would improve the treatment of MDD is the expansion of access to care. Efforts to address the treatment gap for mental disorders have been commissioned by international bodies, including the Comprehensive Mental Health Action Plan 2013–2030 by the WHO, which includes global targets for member states such as increasing service coverage for mental health conditions by at least half by 2030 (ref. 285). Digital technologies could also be used to improve access to care for mental health conditions. Digital technologies offer great promise in delivering highly scalable psychotherapeutic interventions, particularly for those with limited availability of or accessibility

to mental health services[286]. Digital technologies permit people with MDD to self-monitor and self-manage, and may also provide innovative solutions to clinical issues related to screening, diagnosis, assessment and monitoring. However, further research is required to address the observed low long-term engagement with such technology and to evaluate effectiveness[287,288].

Diagnosis and conceptualization

MDD conceptualization and classification require improvement. The elucidation of MDD subtypes based on biological mechanisms, symptoms or both promises to benefit treatment by providing clinicians with further individualization regarding treatment strategies, including medication selection, and may provide greater precision regarding treatment response, prognosis and risk of recurrence. Several attempts have been made to subtype MDD, for example, into melancholic and atypical subtypes[289,290]. The field of precision psychiatry offers promise in using diverse biological markers, such as immunometabolic markers (for example, chronic low-grade inflammation, dyslipidaemia)[290], brain imaging (for example, resting-state functional MRI)[291] and omics-based analysis (such as metabolomics, genomics, transcriptomics) for this task but has not yet affected practice. Clinical formulations that assess symptoms based on the DSM/ICD frameworks and other factors, including development, social, personality and life events, remain the most pragmatic manner to individualize care and select treatment approaches[292]. Another option is to apply a clinical staging model of care[293], whereby treatment is directed on a continuum from the at-risk or latency stage through to late-stage or end-stage disease. Clinical staging can help in predicting required care. For example, patients in the early stage of their illness could benefit from psychoeducation, supportive therapy or self-help strategies, whereas those in more advanced stages could require more intensive interventions such as combination therapies or hospitalization.

Identification of biological mechanisms

Several mechanistic pathways are implicated in MDD although further research is needed to better understand their hierarchy and interaction. With the availability of multiple omics analyses as well as 'big data' sources, including digital health records and smartphone analytics, the emergence of analyses that harness highly dimensioned data sets such as artificial intelligence and machine learning offer promise in predicting susceptibility to illness, identifying depression subtypes and/or guiding personalized treatment selection[25,294]. Owing to the substantial inter-individual variably in the presentation and disease course of MDD, such approaches offer great promise in delivering personalized treatment. A growing number of studies have used such an approach in psychiatry; however, further work is required to address many pertinent questions in the field relating to implementation (such as data privacy concerns and clinician uptake) and technical (such as external validation) considerations[294].

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