Major depressive disorder

Christian Otte[1], Stefan M. Gold[1,2], Brenda W. Penninx[3], Carmine M. Pariante[4],
Amit Etkin[5], Maurizio Fava[6], David C. Mohr[7] and Alan F. Schatzberg[5]

Abstract | Major depressive disorder (MDD) is a debilitating disease that is characterized by depressed mood, diminished interests, impaired cognitive function and vegetative symptoms, such as disturbed sleep or appetite. MDD occurs about twice as often in women than it does in men and affects one in six adults in their lifetime. The aetiology of MDD is multifactorial and its heritability is estimated to be approximately 35%. In addition, environmental factors, such as sexual, physical or emotional abuse during childhood, are strongly associated with the risk of developing MDD. No established mechanism can explain all aspects of the disease. However, MDD is associated with alterations in regional brain volumes, particularly the hippocampus, and with functional changes in brain circuits, such as the cognitive control network and the affective–salience network. Furthermore, disturbances in the main neurobiological stress-responsive systems, including the hypothalamic–pituitary–adrenal axis and the immune system, occur in MDD. Management primarily comprises psychotherapy and pharmacological treatment. For treatment-resistant patients who have not responded to several augmentation or combination treatment attempts, electroconvulsive therapy is the treatment with the best empirical evidence. In this Primer, we provide an overview of the current evidence of MDD, including its epidemiology, aetiology, pathophysiology, diagnosis and treatment.

Major depressive disorder (MDD) is a debilitating disease that is characterized by at least one discrete depressive episode lasting at least 2 weeks and involving clear-cut changes in mood, interests and pleasure, changes in cognition and vegetative symptoms. BOX 1 describes the current diagnostic criteria and specifiers (which enable clinical subtyping) of MDD according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), which was released in 2013 (REF. 1). The cluster of symptoms that characterize a major depressive episode and MDD overlap with depressive symptoms in schizophrenia and bipolar disorder; the application of exclusion criteria enables a diagnosis of MDD.

MDD occurs about twice as often in women than in men[2] and affects about 6% of the adult population worldwide each year[3]. Among all medical conditions, MDD is the second leading contributor to chronic disease burden as measured by 'years lived with disability' (REF. 4). In addition, MDD is associated with an increased risk of developing conditions such as diabetes mellitus, heart disease and stroke[5], thereby further increasing its burden of disease. Furthermore, MDD can lead to death by suicide. It is estimated that up to 50% of the 800,000 suicides per year worldwide occur within a depressive episode[6] and patients with MDD are almost 20-fold more likely to die by suicide than the general population[7].

The genetic contribution to MDD is estimated to be approximately 35%, with higher heritability shown in family and twin-based studies than single-nucleotide polymorphism-based estimates from genome-wide association studies (GWAS). This finding suggests that other genetic variables, such as rare mutations, contribute to MDD risk[8]. In addition, environmental factors, such as sexual, physical or emotional abuse during childhood, are strongly associated with the risk of developing MDD[9], although our understanding of how environmental factors interact with genetic and epigenetic factors is far from complete.

Despite advances in our understanding of the neurobiology of MDD, no established mechanism can explain all aspects of the disease. However, MDD is associated with smaller hippocampal volumes as well as changes in either activation or connectivity of neural networks, such as the cognitive control network and the affective–salience network[10]. Moreover, alterations in the main neurobiological systems that mediate the stress response are evident in MDD, including the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system and the immune system[11].

Both psychotherapy and psychopharmacology are effective in treating MDD. However, approximately 30% of patients do not remit from MDD, even after several treatment attempts[12,13]. New developments in

Correspondence to C.O.
Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany.
christian.otte@charite.de

Author addresses

[1]Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany.

[2]Institute of Neuroimmunology and Multiple Sclerosis (INIMS), University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

[3]Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands.

[4]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

[5]Department of Psychiatry and Behavioural Sciences, Stanford University School of Medicine, Palo Alto, California, USA.

[6]Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA.

[7]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA.

psychotherapy include the use of behavioural intervention technologies. With regard to pharmacological approaches, glutamatergic antidepressants, such as ketamine, are currently under scientific scrutiny after promising initial findings of efficacy.

In this Primer, we provide an overview of the current evidence of MDD, including its epidemiology, aetiology, pathophysiology, diagnosis and treatment. We also outline the key outstanding research questions in the field that should be addressed in the coming years.

Epidemiology

Prevalence and main correlates

A best estimate of the worldwide MDD prevalence comes from the World Mental Health (WMH) Survey, which assessed the DSM-IV criteria for MDD among almost 90,000 individuals in 18 countries from every continent[3]. The average 12-month prevalence of MDD is approximately 6%, which is in line with estimates from earlier large-scale international studies[3]. Lifetime MDD prevalence is typically threefold higher than the 12-month prevalence, indicating that MDD affects one in every six adults[3]. Although lifetime prevalence is an unreliable metric as it probably suffers from recall bias and underestimation[14,15], it indicates that about 20% of all people fulfil the criteria for MDD at some point in their lifetime.

The 12-month MDD prevalence in the WMH Survey ranged from 2.2% in Japan to 10.4% in Brazil (FIG. 1). Although estimates varied substantially across countries for reasons that probably involve both substantive and methodological processes, the 12-month MDD prevalence was found to be similar in ten high-income (5.5%) and eight low-income and middle-income (5.9%) countries, showing that MDD is not just a 'modern-world' health condition. In addition, the median age of onset, severity, symptom profile and basic socio-demographic and environmental correlates (such as sex, education and life events) of MDD are mostly comparable between countries and cultures[16,17]. The discrepancy between countries is evident in terms of the resources and treatments available. In high-income countries, approximately 50–60% of all people with severe MDD receive proper treatment[18,19], whereas in low-income countries <10% of patients do[18].

Women have a twofold increased risk of developing MDD than men after puberty[2]. This disparity reflects the more-frequent occurrence of episodes in women, rather than longer episode duration, differential treatment response or higher recurrence rates in women compared with men[20,21]. In both sexes, the median reported age of onset of MDD is approximately 25 years and the peak risk period for MDD onset ranges from mid-to-late adolescence to early 40s[3]. These findings are in line with observations that, especially in high-income countries, the MDD prevalence generally modestly decreases with age after early adulthood[16].

Other consistently reported environmental determinants of MDD in both men and women are the absence of a partner (for example, owing to divorce or widowhood) and the experience of recent negative life events, such as illness or loss of close relatives or friends, financial or social problems and unemployment[3,22]. In addition, a range of social determinants (including childhood adversities, socioeconomic status and low social support) as well as low educational attainment[23] significantly increases the risk of MDD in men and women (BOX 2). However, the cause–effect relationship between lower educational attainment and MDD is unclear and a large study with 25,000 individuals recently suggested that it might partly be due to shared genetics[24]. Individuals with a history of childhood trauma have a more than twofold increased risk of developing MDD[25]. Furthermore, patients with MDD and a history of childhood trauma show higher symptom severity, a poorer course and more treatment non-response than patients with MDD without childhood trauma[26].

Disease course

The course of MDD is pleomorphic, with considerable variation in remission and chronicity; higher symptom severity, psychiatric comorbidity and a history of childhood trauma all predict a less favourable course[21,26]. In population-based samples, the mean episode duration varies between 13 and 30 weeks and approximately 70–90% of patients with MDD recover within 1 year[27–29]. However, in outpatient care settings, the course is less favourable: only 25% remit within 6 months and >50% of patients still have MDD after 2 years[21,30,31]. After MDD remission, residual symptoms and functional impairment often remain[32]. In addition, the chance of MDD recurrence is high, as about 80% of patients in remittance experience at least one recurrence in their lifetime[33]. The course trajectory in adults seems to be slightly less favourable with increasing age than in younger patients[21].

Disease burden

The Global Burden of Disease Consortium found that, in 2013, MDD was the second leading contributor to global disease burden, as expressed in disability-adjusted life years, in both developed and developing countries[4].

Moreover, the consequences of MDD extend to physical health. Large-scale longitudinal studies converge in their findings suggesting that MDD increases the risk of diabetes mellitus, heart disease, stroke, hypertension, obesity, cancer, cognitive impairment and Alzheimer disease[34] (FIG. 2). Both in the general population and in populations with specific medical illnesses, MDD increases the mortality risk by 60–80%[35,36]. Indeed, the contribution of MDD to all-cause mortality is 10%.

Mechanisms/pathophysiology

Despite advances in our understanding of the neurobiology of MDD, currently no established mechanism can explain all facets of the disease. Animal models of MDD are available and have enabled the discovery of many potentially implicated pathways (BOX 3), although the applicability of these findings in humans is still nascent. Accordingly, we restrict our description to pathophysiological models of MDD that are supported by findings from clinical studies, giving preference to aspects that have been confirmed in meta-analyses and pathways that have been targeted in clinical trials (ideally also with a meta-analysis level of evidence).

Genetics

We have known for more than a century that MDD clusters within families. First-degree relatives of patients with MDD show a threefold increased risk of MDD and heritability for this disorder has been quantified as approximately 35%[37]. Furthermore, genetic overlap between MDD and other psychiatric disorders, such as schizophrenia and bipolar disorder, has been identified[38,39]. However, the search for main genetic effects in MDD so far has not revealed consistent or replicated significant findings[40], as indicated by a large-scale analysis of various GWAS that included 9,240 cases and 9,519 controls[41]. Similarly sized studies of other psychiatric conditions such as schizophrenia, which has higher heritability than MDD, have convincingly implicated at least some genetic loci; for schizophrenia, 108 independent genome-wide significant loci have been shown[42]. Risk of MDD is highly polygenic and involves many genes with small effects[43], which coupled with the heterogeneity of MDD phenotypes requires very high numbers of patients to find significant associations. A recent genome-wide association study in Chinese patients in which a more homogeneous phenotypic approach (recurrent MDD requiring outpatient care) was applied was able to confirm two genome-wide significant genetic loci[44]. Moreover, 15 genetic loci with genome-wide significance have been associated with risk of self-reported MDD in 75,607 patients and 231,747 controls of European descent[45]. Furthermore, some recent studies in >100,000 subjects have also indicated several genome-wide significant loci for neuroticism, a phenotype that is strongly correlated to MDD[46,47]. This finding holds promise for the ongoing search for consistent genetic variants that contribute to MDD risk in a collaborative genome-wide association study carried out by the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc).

Environmental factors

Early epidemiological studies focused on stressful events that are temporally related to MDD, usually in the year preceding onset; the main documented events (such as loss of employment, financial insecurity, chronic or life-threatening health problems, exposure to violence, separation and bereavement)[48] occur most often in adulthood. However, more-recent evidence has focused on exposure to events in childhood as antecedent of MDD later in life. These events include physical and sexual abuse, psychological neglect, exposure to domestic violence or early separation from parents as a result of death or separation, with clear evidence of a dose–response relationship between the number and severity of adverse life events and the risk, severity and chronicity of MDD[9].

Box 1 | Definition of MDD according to DSM-5

- An individual will show five (or more) of the following symptoms, which should be present during the same 2-week period nearly every day and should represent a change from previous functioning:
  - Depressed mood*
  - Markedly diminished interest or pleasure in all, or almost all, activities*
  - 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, which might be delusional; that is, not merely self-reproach or guilt about being sick
  - Diminished ability to think or concentrate, or indecisiveness
  - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan; the individual has made a suicide attempt or a specific plan for committing suicide

- The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning

- The episode is not attributable to the physiological effects of a substance or to another medical condition

- The occurrence of the episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder or other psychotic disorders

- The individual has never had a manic episode or a hypomanic episode

Specifiers of major depressive disorder (MDD) according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th edition[1]) are:

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

*Depressed mood and/or diminished interest or pleasure must be evident for a diagnosis.

The HPA axis is at the centre of the comprehensive neurobiological model that seeks to explain the long-lasting consequences of early trauma. Many animal studies have shown that early-life stress produces persistent increases in the activity of corticotropin-releasing hormone (CRH)-containing neural circuits[49]. This finding is supported by clinical studies showing that individuals who have been sexually or physically abused in childhood show, as adults, a markedly enhanced activity of the HPA axis when exposed to standardized psychosocial stressors or following endocrine tests that attempt to suppress HPA activity[50]. Indeed, glucocorticoid receptor function is reduced in these individuals (so-called glucocorticoid resistance), a finding that is supported by the fact that these individuals also show increased activation of the inflammatory system, which is under physiological inhibitory control by cortisol. Indeed, glucocorticoid resistance, HPA axis hyperactivity and increased inflammation are all evident in MDD (FIG. 3).

Furthermore, *in utero* stress has also been shown to increase the risk of MDD later in life[51]. This novel but burgeoning area of research is providing further evidence of the neurodevelopmental origin of MDD and the long-lasting effects of environmental insults at the earliest stages of life[52].

Gene–environment interactions

The lack of consistent and replicated findings in GWAS for MDD can at least partly be explained by the fact that relevant genetic variants confer an increased risk only in the presence of exposure to stressors and other adverse environmental circumstances — the so-called gene–environment (G×E) interaction (FIG. 4). However, although several potential candidate genes, such as sodium-dependent serotonin transporter (*SLC6A4*), CRH receptor 1 (*CRHR1*) and the gene encoding peptidyl-prolyl *cis-trans* isomerase (*FKBP5*) have been identified, differences in the timings and the type of adverse environmental circumstances have hampered replication studies of single candidate genes.

Epigenetics. Interestingly, studies investigating the molecular mechanisms underlying G×E interactions have shown that they might involve epigenetic regulation[53]. For example, allele-specific, stress-dependent DNA demethylation in glucocorticoid-response elements of a polymorphism in *FKBP5* has been observed[54]. This interaction leads to increased *FKBP5* expression in response to stress, which in turn leads to glucocorticoid receptor resistance[55].

Furthermore, several studies have shown consistent epigenetic changes in the brains of animal models of MDD as well as in post-mortem brain samples of patients with MDD, especially suicide victims who were exposed to early-life adversities[56]. Initial hypothesis-driven studies examined genes involved in the stress response, but more-recent unbiased GWAS have implicated epigenetic changes in genes that are often unrelated to established candidates, therefore, implicating alternative pathophysiological mechanisms, such as cell adhesion and cell plasticity[54]. However, enthusiasm for epigenetic research in MDD is still limited by the small magnitude of the described epigenetic changes (often <10%), especially in comparison with other medical disorders, such as cancer[53].

Neuroendocrinology

As mentioned, the HPA axis is among the most researched biological systems in MDD[57,58]. For example, two meta-analyses[50,59] concluded that cortisol levels in patients with MDD were increased, with a moderate effect size. Importantly, HPA alterations correlate with impaired cognitive function[60] in these patients, and are more common and more pronounced in severely depressed patients with melancholic and/or psychotic features[61] and in elderly patients who have MDD[62]. Furthermore, several studies have prospectively shown that increased levels of cortisol is a risk factor for subsequent MDD in at-risk populations[63,64]. Finally, a study using data from a primary care database including >370,000 individuals indicated that treatment with synthetic glucocorticoids is associated with an increased risk for suicide (approximately sevenfold), MDD (approximately twofold) and other severe neuropsychiatric disorders, even when controlling for the underlying medical disorder[65].

Despite these findings, data from interventional studies are less clear. For example, antidepressants reduce the levels of cortisol in patients with MDD over the course of the treatment[66]. However, a meta-analysis has shown that, independent of improved psychopathology, approximately 50% of patients had similar cortisol levels before and after treatment. Increased levels of CRH in the cerebrospinal fluid (CSF) have been shown in patients with MDD[67] and, accordingly, several randomized controlled trials have examined CRH antagonists in the treatment of MDD. However, the
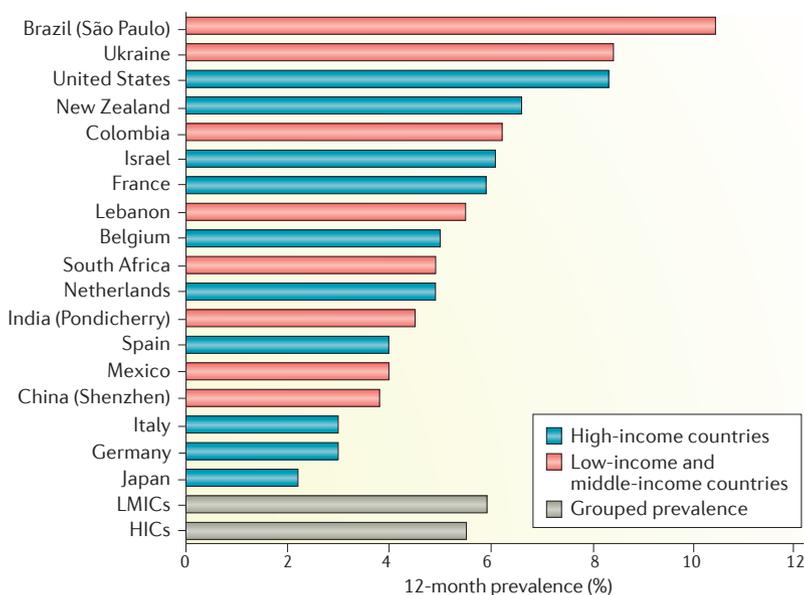

Figure 1 | **Average 12-month prevalence of MDD.** Although considerable variation in inter-country prevalence of major depressive disorder (MDD) is noted, the overall estimates in high-income countries (5.5%) and low-income and middle-income countries (LMICs; 5.9%) are not different. Data from REF. 3.

Box 2 | **Social and environmental determinants of MDD**

Several social and environmental factors are associated with the risk and the outcome of major depressive disorder (MDD)[208]. They can be categorized as demographic factors (for example, age, sex and ethnicity), socioeconomic status (for example, poverty, unemployment, income inequality and low education), neighbourhood factors (for example, inadequate housing, overcrowding, neighbourhood violence and safety), socioenvironmental events (for example, natural disasters, war, conflict, migration, discrimination, difficulties in work, low social support, trauma and negative life events) and lifestyle factors (for example, alcohol use, smoking behaviour, a high-fat or high-sugar diet and physical inactivity). A bidirectional association between these determinants and MDD is evident; certain social variables, such as low socioeconomic status or lack of social support, can contribute to the risk for MDD (a so-called social cause). By contrast, patients with MDD, especially those with a chronic course of the disease, often deteriorate in their social functioning, leading to work and family problems (experiencing 'social drift'), which may eventually lead to poverty[208,222].

overall results have not indicated a major role for CRH antagonists in the treatment of MDD[68]. Clinical trials using glucocorticoid-lowering compounds, such as metyrapone, have also yielded mixed results[69,70]. Fludrocortisone, a mineralocorticoid receptor agonist, has been shown to accelerate the onset of action of standard antidepressants in one randomized controlled trial[71] and to improve cognitive function in patients with MDD in an experimental study[72]. In MDD with psychotic features, the glucocorticoid receptor antagonist mifepristone (also known as RU-486) was shown to ameliorate psychotic symptoms, although secondary analyses of failed trials indicated that very high doses might be required to reach therapeutic blood levels[58].

In summary, although there is unequivocal evidence of HPA alterations in MDD, this has not yet led to new therapeutic avenues. Deeper clinical and biological phenotyping of MDD will lead to the identification of MDD subtypes of patients who are more likely to respond to a given treatment within the HPA axis.

Inflammation

The immune system is an important component of the physiological stress-sensing pathways and closely interacts with the body's main integrative systems (the HPA axis, the autonomic nervous system and the central nervous system (CNS)) in mutually regulatory feed-forward and feedback loops (FIG. 5). A role for peripheral immune dysfunction and neuroimmunological mechanisms in MDD has been supported by a large body of evidence from animal studies (BOX 3). These models have also provided intriguing insights into how peripheral cytokines can, directly and indirectly, affect brain circuits, behaviour and mood. Peripheral cytokines can be transported through the blood–brain barrier to act directly on CNS-resident cells, including astrocytes, microglia and neurons. In addition, inflammatory signals can be conveyed to the CNS through cellular mechanisms (CNS infiltration by peripheral immune cells) or signalling via the vagus nerve (the 'inflammatory reflex'). Animal models have shown that these routes converge in the CNS to alter molecular programmes (for example, receptor expression), neurogenesis and plasticity[73]. Clinical observations suggest that similar mechanisms of inflammation might also be relevant for the development of MDD in patients. For example, a population-based study has shown that both prior severe infections and autoimmune diseases increase the risk of subsequently developing MDD[74]. In addition, patients who receive cytokine treatments, such as IL-2 or interferon-γ (IFNγ), as part of their treatment for hepatitis virus infection or cancer often develop depressive symptoms[75]. Finally, patients with MDD show increased serum levels of cytokines, such as tumour necrosis factor (TNF) and IL-6, as confirmed by meta-analyses[76,77].

Increased expression of genes involved in IL-6 signalling in peripheral blood cells has also been observed in a large-scale cohort study of patients with MDD compared with healthy controls[78]. There have also been a few large, prospective studies indicating that increased levels of IL-6 during childhood significantly increases the risk of developing MDD in adulthood[79]. Recent studies using PET imaging[80] as well as analyses of post-mortem brain tissue[81] have indicated neuroinflammation and microglial activation in the CNS of patients with MDD. Finally, a potential role for inflammation in MDD is also supported by clinical trials of NSAIDs, reviewed in a meta-analysis[82].

Neuroplasticity

The peripheral changes in cortisol levels and inflammatory mechanisms might ultimately induce depressive symptoms by affecting brain function at a cellular level, primarily by disrupting neuroplasticity and, accordingly, neurogenesis — the process by which new neurons are generated in the adult brain from pluripotent stem cells. Along these lines, lower levels of the neurotrophin brain-derived neurotrophic factor (BDNF) have been measured in the sera of patients with MDD. BDNF and other regulators of neuroplasticity might affect behaviour through their control of neurogenesis. *BDNF* mRNA levels are also reduced in the leukocytes of patients with MDD, and pharmacological and non-pharmacological antidepressant therapies have been shown to normalize BDNF levels[83].

Although BDNF and other correlates of neuroplasticity have been implicated, the precise role of neurogenesis in MDD has been debated[84]. For example, reducing adult neurogenesis in rodents in the absence of stress does not induce depressive-like behaviour. However, reduced neurogenesis can precipitate depression-like symptoms in the context of stress. At a biological level, adult neurogenesis promotes resilience to stress by enhancing glucocorticoid-mediated negative feedback on the HPA axis[84]. Importantly, in rodents, effective adult neurogenesis occurs following antidepressant treatment that reduces stress responsiveness[84]. Thus, it is biologically plausible that neurogenesis contributes to the clinical effects of antidepressants in humans.

Monoamines

The monoamine neurotransmitters serotonin (also known as 5-hydroxytryptamine), noradrenaline and dopamine were first implicated in MDD after it was discovered that substances such as the antihypertensive
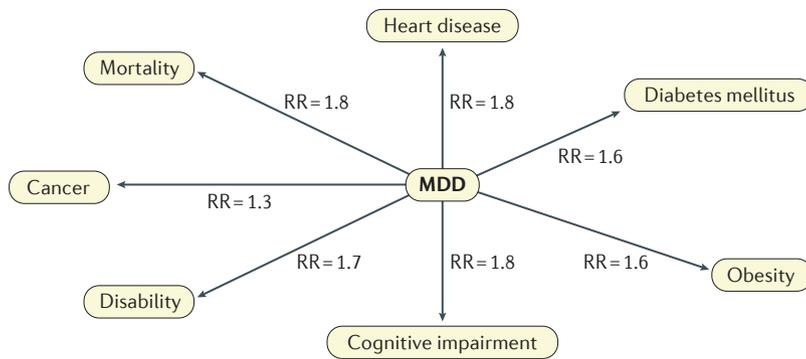
Figure 2 | **The somatic consequences of MDD.** Evidence from meta-analyses[34] of longitudinal studies has revealed that the relative risk (RR) of various diseases is increased in those with major depressive disorder (MDD) compared with those who do not have MDD. The mechanisms that contribute to the diverse somatic consequences of MDD are complex and together might explain the unfavourable health outcomes in patients with MDD. They include unhealthy lifestyle, poorer care (or selfcare) adherence, adverse effects of medications and shared pathophysiology (for example, upregulation of immune–endocrine stress systems, which is present in MDD but also in obesity). These contributions are explained in more detail elsewhere[5,34].

drug reserpine reduce their levels and that some patients taking these drugs developed MDD[85]. The role of monoamines in MDD was further supported by the discovery in the 1950s and, later, the mechanistic interrogation of the first antidepressant drugs — tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Both TCAs and MAOIs have robust effects on monoamine neurotransmission; TCAs block the reuptake of monoamines in the presynaptic neuron and MAOIs prevent their breakdown once reabsorbed, enhancing the effects of the neurotransmitters. These findings stimulated the development of a long series of monoamine-based compounds, which continue to dominate the field of modern psychopharmacology of MDD.

However, many studies that have measured noradrenaline and serotonin metabolites in the plasma, urine and CSF, as well as post-mortem studies of the brains of patients with MDD have yielded inconsistent results (reviewed in REF. 86). Furthermore, drugs that target monoamines affect these neurotransmitter systems within hours after administration. However, the antidepressant effects are often only evident after several weeks of treatment. Changes in brain gene expression that occur after continuous treatment with drugs that target monoamines might underlie their therapeutic effects[87], rendering the monoamine hypothesis of MDD overly simplistic.

Structural brain alterations

It stands to reason that a combination of the molecular and cellular mechanisms of the pathobiology reviewed above might ultimately contribute to morphological changes in brain structure in MDD as detected by neuroimaging. Indeed, many cross-sectional studies using structural brain imaging have investigated regional brain volumes in patients with MDD. Although smaller volumes in many different brain areas have been reported in individual case–control studies, the best and most consistent evidence from structural MRI studies support that hippocampal volume is reduced in individuals with MDD. For example, a meta-analysis of 143 studies[88] confirmed smaller volumes in patients with MDD than in healthy controls in the basal ganglia, thalamus, hippocampus and several frontal regions (FIG. 5). A meta-analysis by the ENIGMA (enhancing neuroimaging genetics through meta-analysis) working group of MRI data from more than a dozen independent research samples detected significantly lower volumes in the hippocampus (but no other subcortical structures)[89] as well as cortical thinning in the orbitofrontal cortex, anterior and posterior cingulate, insula and temporal lobes in patients with MDD[90].

Furthermore, a large-scale trans-diagnostic voxel-based morphometry meta-analysis of 193 studies comprising 15,892 individuals also suggested that the hippocampus might be selectively affected in MDD compared with other psychiatric disorders, such as schizophrenia, bipolar disorder, addiction, obsessive–compulsive disorder and anxiety[91]. Although an earlier meta-analysis suggested that smaller hippocampal volumes might already be present in patients with first-episode MDD[92], this could not be confirmed in the most recent meta-analysis of MRI data by the ENIGMA working group[89]. Thus, whether smaller volumes of the hippocampus seen in MDD are an early manifestation or whether they develop later in the course of the disorder remains unclear.

Functional brain circuits

Several studies have suggested that stress-associated alterations in inflammatory and glucocorticoid signalling are associated with corresponding functional changes in multiple brain networks[93,94]. Indeed, neuroimaging studies in MDD have identified abnormalities in either activation or connectivity within the affective–salience circuit, the medial prefrontal–medial parietal default mode network and the frontoparietal cognitive control circuit.

Affective–salience circuit. The affective–salience circuit plays a central part in guiding motivated behaviour, whether related to emotional or cognitive stimuli, and includes projections between the dorsal cingulate, anterior insula, ventral striatum and amygdala, as well as downstream targets, such as hypothalamic and brain stem nuclei.

One of the most frequently reported neuroimaging findings in MDD is abnormally increased connectivity and heightened activation of the amygdala[95]. In addition, much like the amygdala, the dorsal anterior cingulate and anterior insula are hyperactive in MDD, which may reflect the increased salience of negative information and self-directed thoughts in MDD[95]. By contrast, decreased activity and connectivity of the ventral striatum and other reward-related regions have been observed in MDD, leading to decreased recruitment of saliency-processing areas, such as the dorsal cingulate and anterior insula[96,97].

Default mode network. The default mode network is characterized by greater activity during 'resting' states in which most mental activity is internal or self-directed. Difficulties in dynamic modulation of the default mode network in MDD has been proposed to underlie excessive self-focus and rumination[95,98]. Indeed, the default mode is hyperconnected in MDD[99], which correlates positively with measures of rumination[100]. By contrast, the dynamic coupling between frontoparietal activation (which increases with task-directed attention) and default mode deactivation is perturbed in MDD[101,102], which might contribute to cognitive deficits in patients with MDD.

The frontoparietal cognitive control circuit. The frontoparietal cognitive control network is engaged across many cognitive tasks[103]. A recent meta-analysis found evidence for frontoparietal hypoconnectivity in MDD, especially of the dorsolateral prefrontal cortex, implicating it in goal-directed attention deficits in MDD[104]. Moreover, decreased frontoparietal connectivity has been shown both at rest and in response to negative stimuli, but not in response to positive stimuli, suggesting that this network may contribute to inappropriate cognitive appraisals of negative events[105,106].

Diagnosis, screening and prevention
Differential diagnosis
According to DSM-5 (BOX 1), MDD is distinguished from normal sadness or bereavement; however, in patients who, for example, are mourning and who develop symptoms that are severe enough and that persist beyond the acute grieving period, an MDD diagnosis can be given. Although it is possible to diagnose MDD on the basis of a single depressive episode of ≥2 weeks, MDD is recurrent in the majority of cases[1].

The key differential diagnoses of MDD are with bipolar disorder, with persistent depressive disorder and with schizophrenia. The differential diagnosis of bipolar disorder rather than MDD rests entirely with the presence of a history of hypomania or mania, which is characterized by a clear period of elevated mood

or irritability, and with at least three of the following symptoms: inflated self-esteem; reduced need for sleep; increased speech; flight of ideas; distractibility; increased activity in goal-directed tasks; and/or involvement in risky behaviour.

Persistent depressive disorder is a chronic disorder and describes patients who have had depressive symptoms for >2 years. Apart from depressed mood, only two of six symptoms (appetite disturbance, sleep disturbance, loss of energy, decreased self-esteem, poor concentration or hopelessness) are required for the diagnosis. Thus, it is possible to meet criteria for persistent depressive disorder without having MDD. If a patient meets criteria for MDD, then the patient would receive two diagnoses — MDD and persistent depressive disorder. Finally, for an MDD diagnosis, the depressive episode must not be better explained by schizophrenia, schizoaffective disorder or other psychotic disorders (BOX 1).

Specifiers of MDD
Once a diagnosis of MDD is made, the condition can be further characterized using various modifiers or specifiers[1] (BOX 1). The first specifier, severity of episode, is rated from mild to moderate to severe. Severe symptoms have a substantial effect on function.

With anxious distress. The specifier 'with anxious distress' was introduced because patients with MDD with considerable co-occurring anxiety are more likely to report suicidal thoughts and be less responsive to traditional antidepressants than others. The specifier requires experience of at least two of the following: a sense of being 'keyed up' or tense; unusual restlessness; trouble concentrating secondary to worry; fear that awful things will happen; and worry about losing self-control. These symptoms need to be present most of the days that the patient experiences an episode of MDD.

With mixed features. The specifier 'with mixed features' reflects an idea that MDD lies on a continuum with bipolar disorder and that patients with either diagnosis can show features of the other during an index episode[1]. This hypothesis is based on the observation that some patients with MDD show rapid thinking and reduced need for sleep, which are characteristic of bipolar disorder. The criteria include experiencing at least three of the following symptoms during the depressive episode: elevated and expansive mood; heightened self-esteem or grandiosity; increased speech or pressure of speech; racing thoughts; increased energy or directed activity; excessive activity in behaviour with possibly negative consequences; and/or reduced need for sleep. A pressing clinical question is whether MDD with mixed features requires a different therapy than MDD without mixed features.

With melancholic features. 'With melancholic features' refers to the presence of what has often been referred to as endogenous features. The criteria include anhedonia,

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Box 3 | The role of animal models in the understanding of MDD

Finding the appropriate model systems for a given human disease is always challenging, particularly for psychiatric disorders[223]. Developing animal models is further complicated by the lack of consistently identified genetic risk factors of depression in humans. Moreover, many of the symptoms typically experienced by patients with major depressive disorder (MDD) are highly subjective (such as depressed mood) and only few can be objectively observed and assessed in animals. Despite these challenges, animal models have enabled the discovery of several target pathways that might contribute to the pathogenesis of MDD and have facilitated the study of the implicated molecular processes. These pathways include but are not limited to neuroendocrine[57] and immune[214] mechanisms, epigenetics[224], molecular networks and the transcriptome[225], the microbiota and the gut–brain axis[226], synaptic dysfunction and plasticity[227] and neurogenesis[228].

Indeed, this fascinating and highly active area of investigation has the potential to uncover novel targets for therapy and ultimately to bring about better treatments for patients. However, the clinical relevance of many of these mechanisms for MDD remains uncertain; no newly developed, hypothesis-driven therapeutic approaches for depression have yet made it to the clinic.

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lack of pleasure and loss of reactivity to positive stimuli, distinct quality of depressed mood (such as despair), depression worse in the morning, waking early in the morning, psychomotor disturbance, weight loss and excessive guilty thoughts.

With atypical features. The specifier 'with atypical features' refers to a set of symptoms that are common in MDD. The criterion of mood reactivity in atypical depression requires that mood brightens in response to actual or potential positive events, which is in contrast
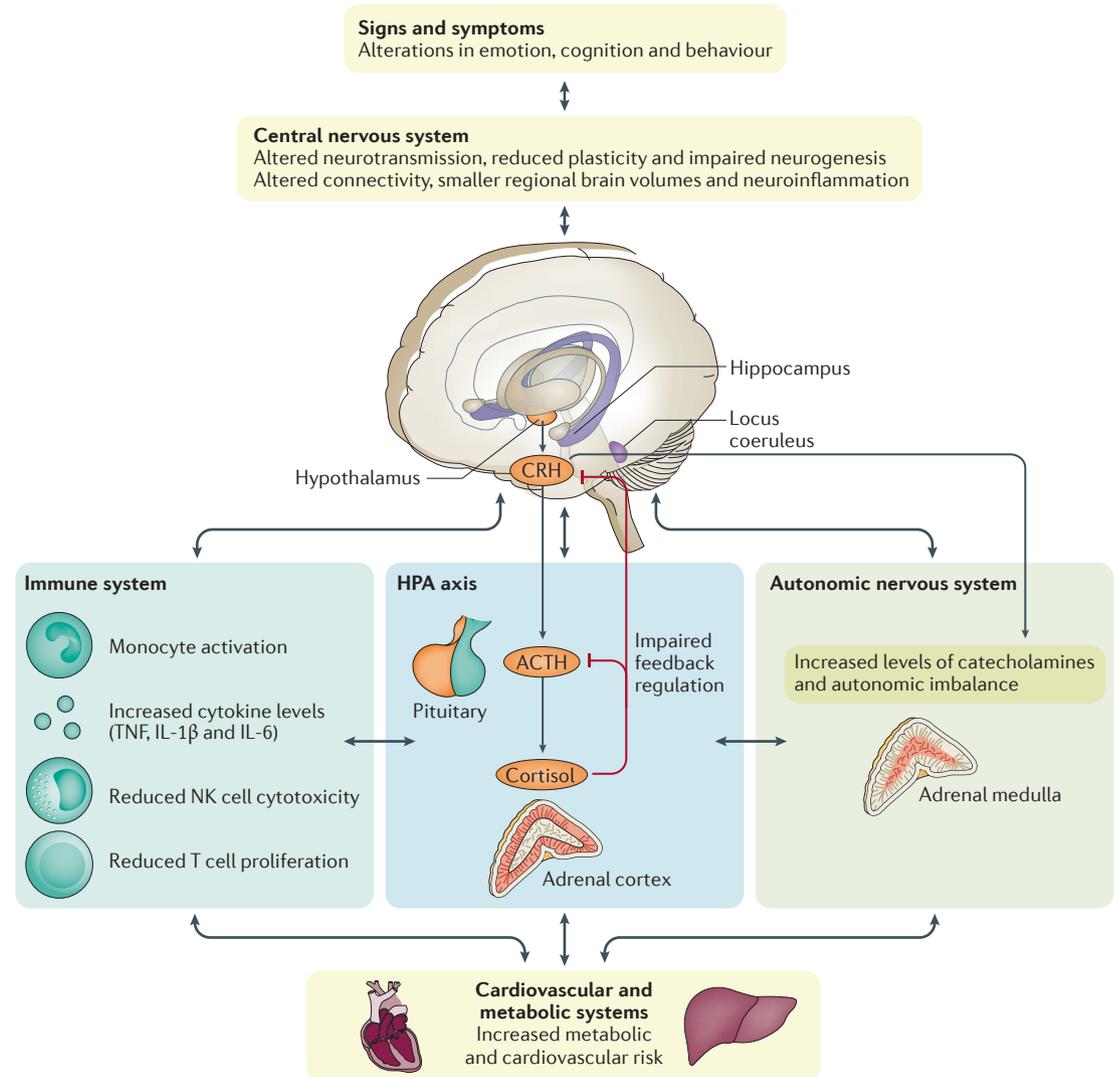

Figure 3 | **Biological systems involved in the pathophysiology of MDD.** Clinical studies in major depressive disorder (MDD) and relevant animal models have identified pathophysiological features in the central nervous system, as well as the major stress response systems, such as the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system and the immune system. In the central nervous system, altered neurotransmission and reduced plasticity are evident. These could underlie functional changes in relevant brain circuits (for example, cognitive control and affective–salience networks), smaller regional brain volumes (for example, in the hippocampus) and neuroinflammation, as confirmed in neuroimaging studies. Beyond the central nervous system, chronic hyperactivity impairs feedback regulation of the HPA axis, which is one of the most consistently reported biological features of MDD. Within the immune system, substantial evidence supports increased levels of circulating cytokines and low-grade chronic activation of innate immune cells, including monocytes. However, other aspects of immunity seem to be impaired as exemplified by reduced natural killer (NK) cell cytotoxicity and T cell proliferative capacity. Once it becomes chronic, both HPA axis hyperactivity and inflammation might converge with alterations in the autonomic nervous system to contribute to central nervous system pathobiology as well as cardiovascular and metabolic disease, which often co-occur with MDD. The sequence of events leading to changes in these interconnected systems and their exact relationship is not known. However, mechanistic studies in animals have shown that alterations in stress response systems can directly and indirectly affect the central nervous system (BOX 3). Conversely, chronic stress and associated changes in behaviour can reproduce many of the stress system alterations, including HPA feedback impairment and inflammation, which suggests a bidirectional link between central and peripheral biological features of MDD. ACTH, adrenocorticotropin; CRH, corticotropin-releasing hormone; TNF, tumour necrosis factor.
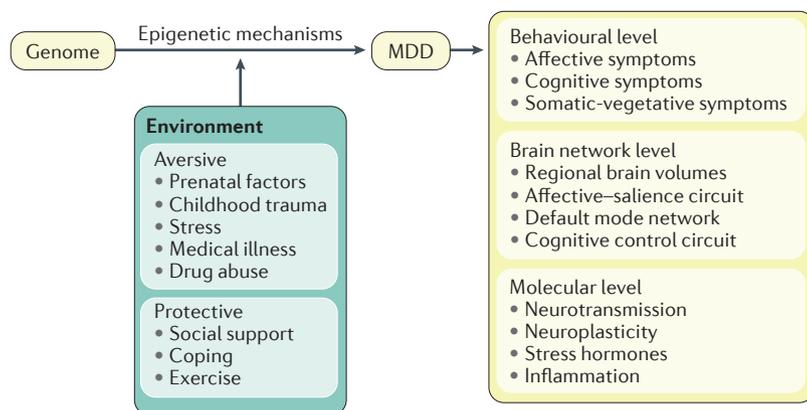
Figure 4 | **Model of gene–environment interactions that lead to MDD.** The schematic depicts a model that is based on predisposing genetic vulnerabilities that interact with aversive and protective environmental factors in the development of major depressive disorder (MDD). At least some of the environmental effects are mediated through epigenetic mechanisms to produce the phenotype of MDD, which is characterized by alterations on a molecular level, on a brain network level and on a behavioural level.

to the 'with melancholic features' specifier. Other criteria for 'with atypical features' include at least two out of the following: significant increase in weight or appetite; increased sleep; a sense of leaden paralysis; and interpersonal sensitivity.

With psychotic features. Previously, the 'with psychotic features' specifier in DSM-IV was included as part of the severity continuum from mild to severe with psychotic features. In DSM-5, psychotic features were separated from the severity specifier because the two were not always highly correlated (that is, mild MDD can also present with psychotic features)[107]. Psychotic features in MDD are mostly mood-congruent, that is, the content of delusions or hallucinations is consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism or deserved punishment. However, mood-incongruent psychotic features that do not include these typical themes can also occur.

With catatonic features. The specifier 'with catatonic features' refers to marked psychomotor disturbance that may involve decreased motor activity, decreased engagement during interview or physical examination, or excessive and peculiar motor activity. These patients are often psychotic.

Research Domain Criteria
In addition to DSM-5, the US National Institute of Mental Health (NIMH) developed the Research Domain Criteria (RDoC) that are not meant to be a diagnostic system but a framework for organizing research. The RDoC approach consists of a matrix in which the rows represent specified functional constructs characterized by genes, molecules, cells, circuits, physiology, self-report and paradigms used to measure it[108]. Constructs are in turn grouped into five higher-level domains of functioning: negative valence systems (encompassing fear, anxiety and loss); positive valence systems (encompassing reward seeking and consummatory behaviour);

cognitive systems; systems for social processes; and arousal and regulatory systems (responsible for generating activation of neural systems as appropriate for various actions and homeostatic control, for example, energy balance and sleep). The ultimate goal of RDoC is to develop a deeper understanding of the biological and psychosocial basis of psychiatric disorders, which might help to improve current classification systems[109].

Screening
Screening is controversial in the MDD field. Many experts argue that screening for depression is of obvious benefit because MDD is often overlooked in medical settings[110]. By contrast, others state that it is impractical to implement universal screening and argue that there is a lack of evidence to support screening[111]. A recent systematic review included 71 studies and assessed the benefits and harms of screening for depression in primary care[112]. The authors concluded that the overall evidence of health benefit of depression screening in primary care is weak. However, the existing data[112] indicate that screening programmes generally increase the likelihood of remission and treatment response in general adult populations, but only in the presence of subsequent treatment offers.

Prevention
Given the high prevalence of MDD, effective prevention strategies such as strengthening protective factors (for example, increasing social support or problem-solving skills) or diminishing prodromal disease stages (such as reducing depressive symptoms before they fulfil criteria for MDD) might have an enormous public health impact in reducing disease burden.

The effects of preventive psychological interventions on the incidence of MDD were systematically examined in a meta-analysis of 32 randomized controlled trials[113]. The meta-analysis included studies examining universal prevention (in a whole population group regardless of risk status), selective prevention (in individuals or subgroups at increased risk of developing depression) and indicated prevention (in individuals identified as having prodromal symptoms of depression). The results indicated a 21% decrease in the incidence of MDD in the prevention groups compared with control groups who did not receive preventive interventions[113]. The authors concluded that prevention of MDD seems feasible and may be an effective way to reduce the numbers of incident MDD cases.

Management
In the management of MDD, there are two main initial treatment options: psychotherapy and pharmacotherapy. Different guidelines concur that moderate-to-severe depressive episodes should be treated with medication or with a combination of medication and psychotherapy[114–117]. By contrast, a mild depressive episode can be initially treated with psychotherapy alone. However, patient preferences and prior treatment history should always be taken into account. Furthermore, in a mild depressive episode it is also possible to pursue an initial strategy of 'watchful waiting' without treatment.
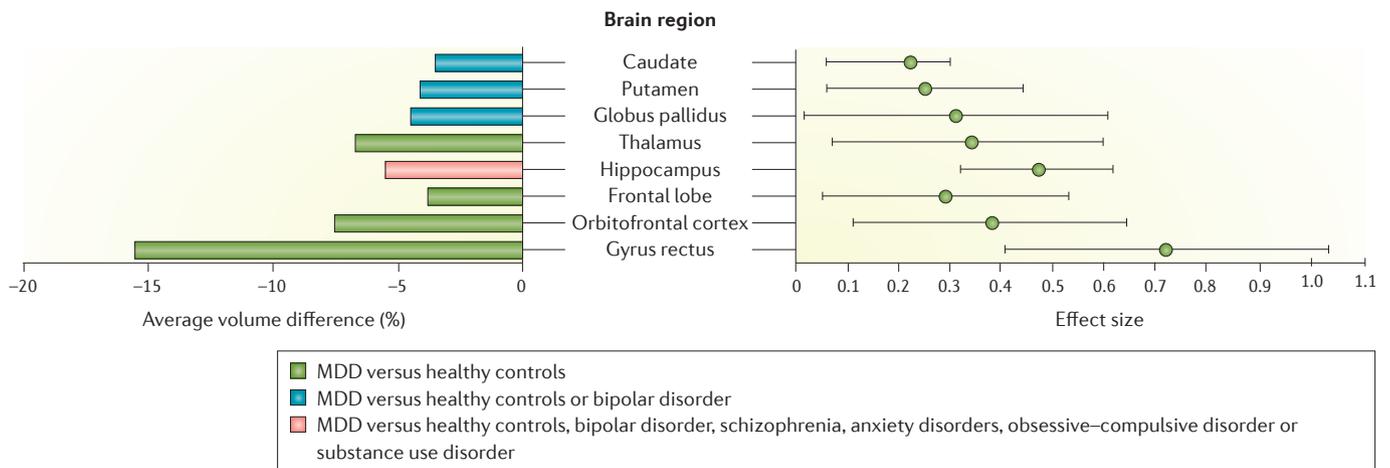
Figure 5 | **Structural brain alterations in MDD.** Regional brain volumes as determined by structural MRI have been investigated in patients with major depressive disorder (MDD) compared with healthy controls in numerous cross-sectional studies. Brain areas with smaller volumes in MDD include the basal ganglia, thalamus, hippocampus and frontal regions, typically with volume differences between 3.5% and 15.5% (left graph) and moderate effect sizes (right graph; error bars indicate 95% confidence intervals). Smaller volumes in the basal ganglia and the hippocampus have also been confirmed when comparing patients with MDD to those with bipolar disorder, suggesting some specificity of these areas for the depressive symptoms that are characteristic of unipolar MDD. Finally, in an independent meta-analysis of structural MRI data using voxel-based morphometry, only smaller volumes in the hippocampus were specific to patients with MDD when compared with other psychiatric disorders. Volume group differences, effect sizes and confidence intervals of MDD compared with healthy controls are based on data from Kempton et al.[88], as are the comparisons of MDD and patients with bipolar disorder. Comparisons of MDD with bipolar disorder, schizophrenia, anxiety disorders, obsessive–compulsive disorder or substance use disorder are based on data from Goodkind et al.[91].

However, this period should not exceed 2 weeks, after which time treatment should be started in case the mild depressive episode has not resolved[116]. FIGURE 6 depicts a stepped-care model, which aims to guide patients, carers and practitioners in their treatment decisions[115].

Psychotherapy

Psychotherapy for MDD comes in many different forms, the most common of which are described in BOX 4. These different paradigms rely on different conceptual models and prescribe techniques that vary to some degree in their focus and methods. A large number of randomized controlled trials and meta-analyses consistently show that psychotherapy is effective in treating MDD; no consistent or clinically meaningful differences are evident between different types of psychotherapy[118–120]. This conclusion[121] has led to two broad hypotheses to explain the efficacy of psychotherapies.

The first hypothesis — the nonspecific or common factors explanation — argues that the primary agents for change in psychotherapy are mainly those that are common to all psychotherapies, such as the therapeutic alliance (a positive, warm, caring and genuine stance)[122] and therapist factors[123]. The common factors approach would suggest that focusing on training and quality assurance for these common factors will optimize treatment outcomes.

By contrast, proponents of the specific-factors explanation argue that treatment-specific strategies produce change via different pathways, such as cognitive restructuring, behavioural activation or improved interpersonal functioning[124]. Accordingly, head-to-head comparisons of different psychotherapeutic treatment models, which are grossly underpowered to detect treatment differences[125], hide patient variables such as the severity of depression, social dysfunction and cognitive dysfunction, which have been shown to differentially predict outcomes for different treatments[126,127]. To the degree that the specific factors hypothesis is true, treatment outcomes might be optimized by tailoring specific interventions to patient characteristics.

Psychotherapy produces effects that are mostly equivalent to pharmacotherapy, although effect sizes from pharmacological and psychotherapeutic trials cannot be readily compared because of methodological issues (for example, blinding)[128]. A recent individual patient data meta-analysis, combining data across 16 trials that compared individual psychotherapy to antidepressant medication, showed no meaningful differences in outcomes on self-reported depression or rates of response or remission[129]. The beneficial effects of cognitive therapy have been shown to persist for at least 1 year post-treatment, which is similar to keeping people on antidepressant medications, and with lower relapse rates than in patients who withdraw from medications[130].

Although psychotherapy is clearly effective, many people have barriers to access, including time constraints, lack of available services and cost[131,132]. Providing psychotherapy over the telephone has been repeatedly shown to be an effective medium for delivering psychotherapy[133], producing outcomes that are equivalent to face-to-face therapy and reducing dropout[134]. Furthermore, group therapy is often recommended as a less costly way of providing treatment, particularly for

patients with mild-to-moderate symptoms[135]. Trials comparing individual to group psychotherapy have shown individual treatment to be moderately superior to group post-treatment, although these differences disappear at 3-month follow-up[136].

Technology-supported care. Behavioural intervention technologies, which use computers, tablets and phones to teach self-management skills[137], are effective at reducing symptoms of MDD, when applied correctly. Although standalone technology-based interventions have not shown consistent benefits, primarily because people with MDD do not adhere to them, internet-based tools, combined with low-intensity coaching via phone or messaging, are highly effective at reducing symptoms of depression[138,139]. Evidence for the efficacy and cost-effectiveness of these coached intervention technologies has led to their being integrated into national mental health services in several countries, including England[140] and Australia[141].

However, well-designed head-to-head comparisons of technology-supported care and more-traditional forms of psychotherapy or pharmacotherapy have yet to be carried out. Accordingly, whether patients can be identified who might respond better to technology-based treatments than to traditional treatments is unclear. Indeed, as attitudes and expectations about the role of technology in daily life change, the patients who are likely to respond to such treatments will probably change. The rapid rate at which technology advances means that technology-based interventions will continue to grow and evolve rapidly[142].

An emerging area of technology is digital phenotyping, which harnesses the growing availability of data generated continuously in the course of daily lives to create behavioural markers related to depression. For example, mobile phones, with a growing complement of sensors, have become personal sensing systems. As people tend to keep their phones with them, phone sensors can continuously estimate the severity of depression in real time[143]. This technology opens the possibility of intervention tools that can detect and react to sensed states and behaviours, enabling just-in-time prompting and reinforcement of treatment-congruent behaviours[144], as well as tools that can passively monitor the risk of depression. Harnessing personal sensing platforms has the potential to shift our treatment tools from episodic to continuous, from reactive to proactive and from provider-centred to patient-centred[145].

Pharmacotherapy

Three decades after monoamine neurotransmitters were implicated in MDD, it became clear that the narrow focus on increasing monoamine levels in the synaptic cleft (by blocking reuptake or degradation of monoamines) was overly simplistic. Now, antidepressants are known to induce neural plasticity and the modulation of monoamines is only the first of their therapeutic effects[146].

Mechanisms of action. Monoamine-based antidepressant drugs are thought to initiate an adaptive neuronal response to the biochemical perturbations in the synapse. Downstream changes in intracellular signalling pathways as well as changes in gene expression and neural and synaptic plasticity (including hippocampal neurogenesis) might have crucial roles in these adaptive changes[147,148], although the exact mechanism by which antidepressants exert their effects remains incompletely understood.

Given the now understood complexity of the activity of these drugs, the usefulness of the standard classification of antidepressant drugs, typically based on the specific effects on individual monoamine neurotransmitters, has been challenged[149]. However, such classification, often reflecting the affinity of drugs for presynaptic and postsynaptic monoamine receptors and/or monoamine transporters, has been useful in understanding some of their adverse effects. An international initiative from five scientific organizations with a focus and expertise in neuropsychopharmacology recently developed the Neuroscience-based Nomenclature[149] of psychotropic drugs that, instead of grouping drugs according to indications (such as antidepressants or antipsychotics), organizes medications on the basis of their known pharmacological actions (such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs)).

In summary, monoaminergic neurotransmission is extremely complex and includes several neurotransmitters, presynaptic and postsynaptic receptors, transporters and enzymes that determine the availability and the effects of the specific monoaminergic transmitter (FIG. 7).
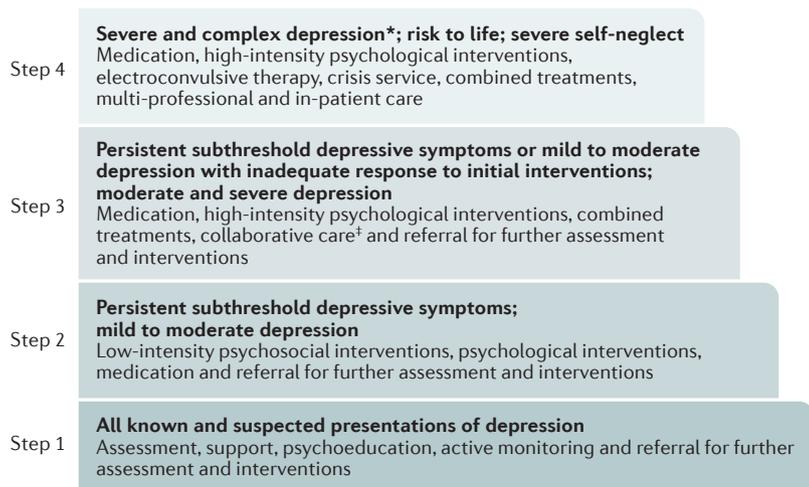

Step 4	**Severe and complex depression*; risk to life; severe self-neglect** Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multi-professional and in-patient care
Step 3	**Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression** Medication, high-intensity psychological interventions, combined treatments, collaborative care‡ and referral for further assessment and interventions
Step 2	**Persistent subthreshold depressive symptoms; mild to moderate depression** Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions
Step 1	**All known and suspected presentations of depression** Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions

Figure 6 | **Stepped-care model in the management of MDD.** The stepped-care model proposes that the least intrusive, most effective intervention is provided first. If the initial intervention shows no benefit or if the individual declines an intervention, an appropriate intervention from the next step should be offered. *Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms and/or is associated with considerable psychiatric comorbidity or psychosocial factors. ‡Only for depression in which the person also has a chronic physical health problem and associated functional impairment. From REF. 115, National Institute for Health and Care Excellence (2009; updated 2016) CG90 Depression in adults: recognition and management. Manchester: NICE. Available from https://www.nice.org.uk/guidance/CG90. Reproduced with permission.

Box 4 | Psychotherapy for MDD

Cognitive–behavioural therapy
Cognitive–behavioural therapy teaches the patient with major depressive disorder (MDD) to identify negative, distorted thinking patterns that contribute to depression and provides skills to test and challenge these negative thoughts, replacing them with more accurate positive ones.

Behavioural activation therapy
Behavioural activation therapy focuses on increasing the patient's positive activities that provide a sense of pleasure or mastery. This treatment also frequently focuses on identifying and confronting avoidance processes.

Psychodynamic therapy
Psychodynamic therapy helps the patient to explore and gain insight into how emotions, thoughts and earlier life experiences have created patterns that contribute to current problems. Recognizing these patterns can help a person to cope and to change those patterns.

Problem-solving therapy
Problem-solving therapy teaches patients a structured set of skills to generate creative methods to address problems, to identify and to overcome potential barriers to goals and to make effective decisions.

Interpersonal therapy
Interpersonal therapy focuses on helping people to identify and to resolve problems in relationships and social roles, including interpersonal conflicts, role transitions and diminished or impoverished relationships.

Mindfulness-based therapy
Mindfulness has its origins in contemplative practices, primarily Buddhism, and involves regular meditative practice in which one pays attention to thoughts, feelings and experiences in a non-judgemental manner, learning to accept things as they are without trying to change them.

Tolerability and efficacy. The success of the SSRIs and SNRIs in displacing TCA drugs as first-choice agents was not based on established differences in efficacy, but rather on a generally more favourable adverse-effect profile, such as lack of anticholinergic and cardiac effects and a high therapeutic index (the ratio of lethal dose to therapeutic dose), combined with ease of administration. However, all of the monoamine-based antidepressant drugs, regardless of their pharmacological class, have fundamentally comparable modest efficacy, with response rates around 50%, and show a characteristic delayed (typically more than several weeks) response to treatment[12,150]. However, the SSRIs and SNRIs are also not devoid of considerable tolerability issues: common acute treatment adverse effects are nausea, insomnia, headaches, dizziness, gastrointestinal symptoms and sexual dysfunction, whereas common long-term adverse effects include weight gain, sexual dysfunction and sleep disturbances[151].

In the past two decades, there have been efforts to develop antidepressant drugs that are not monoamine-based, that are devoid of some of the untoward effects of these drugs and that are able to induce clinical changes in a much more rapid manner. Compounds that are under development include neurokinin 1 antagonists[152], glutamatergic system modulators[153], anti-inflammatory agents[154], opioid tone modulators and opioid-κ antagonists[155], hippocampal neurogenesis-stimulating treatments[156] and antiglucocorticoid therapies[157]. The degree of advancement in the development process varies across these different mechanisms, although all of these types of compounds have shown some degree of promise in the treatment of MDD.

Combined pharmacotherapy and psychotherapy
Several studies have shown that initiating treatment with both psychotherapy and pharmacotherapy produces significantly better outcomes than either treatment alone[158,159]. Similarly, augmenting psychotherapy or antidepressant medications with the treatment not received when the monotherapy has not achieved satisfactory results is also effective at increasing the response rate[160].

Treatment-resistant depression
The term treatment-resistant depression (TRD) is typically used to describe a form of MDD that has not responded adequately to at least one antidepressant[161], although varying definitions of treatment resistance exist[162]. TRD is frequently observed in clinical practice, with up to 50–60% of patients not obtaining adequate response following a first antidepressant drug treatment[161]. A careful diagnostic re-assessment is considered crucial to the proper management of patients with TRD. More specifically, it is important to evaluate the potential role of several contributing factors, such as medical and psychiatric comorbidity. The degree of resistance to treatment can vary greatly among patients with TRD and some staging methods to classify TRD on the basis of different levels of treatment resistance have been shown to be of use clinically[163]. A meta-analysis showed several variables are associated with treatment resistance, including old age, marital status, long duration of current depressive episode, moderate-to-high suicidal risk, anxious comorbidity, high number of hospitalizations and comorbid personality disorders[164].

The most established strategies for treating TRD include psychopharmacological approaches, psychotherapy and electroconvulsive therapy (ECT).

Psychopharmacological strategies. Psychopharmacological approaches for TRD involve high-dose drug therapy or combination therapy. For example, the term high-dose treatment refers to a psychopharmacological strategy involving the considerable increase (doubling or tripling) of the dose of the antidepressant in the face of non-response, a strategy that has been shown to lead to significant improvements particularly in the event of partial response. This strategy has recently been confirmed in two meta-analyses looking at SSRI use[165,166].

In addition, the strategy of switching involves changing the primary antidepressant drug to another of the same class or of a different class. In the STAR*D study,

this strategy led to remission in one in four patients who were citalopram (an SSRI) non-responders (both within the same class or within a different class), but its success in patients who have not responded to two anti-depressant trials is extremely modest, with only one in ten patients achieving remission[12].

Another approach in TRD is augmentation, in which ongoing antidepressant drug treatment is combined with non-antidepressant drugs. Initially well-studied augmentation strategies, such as lithium or L-triiodothyronine (T3)[167], have become somewhat less common in practice, whereas augmentation with atypical antipsychotic
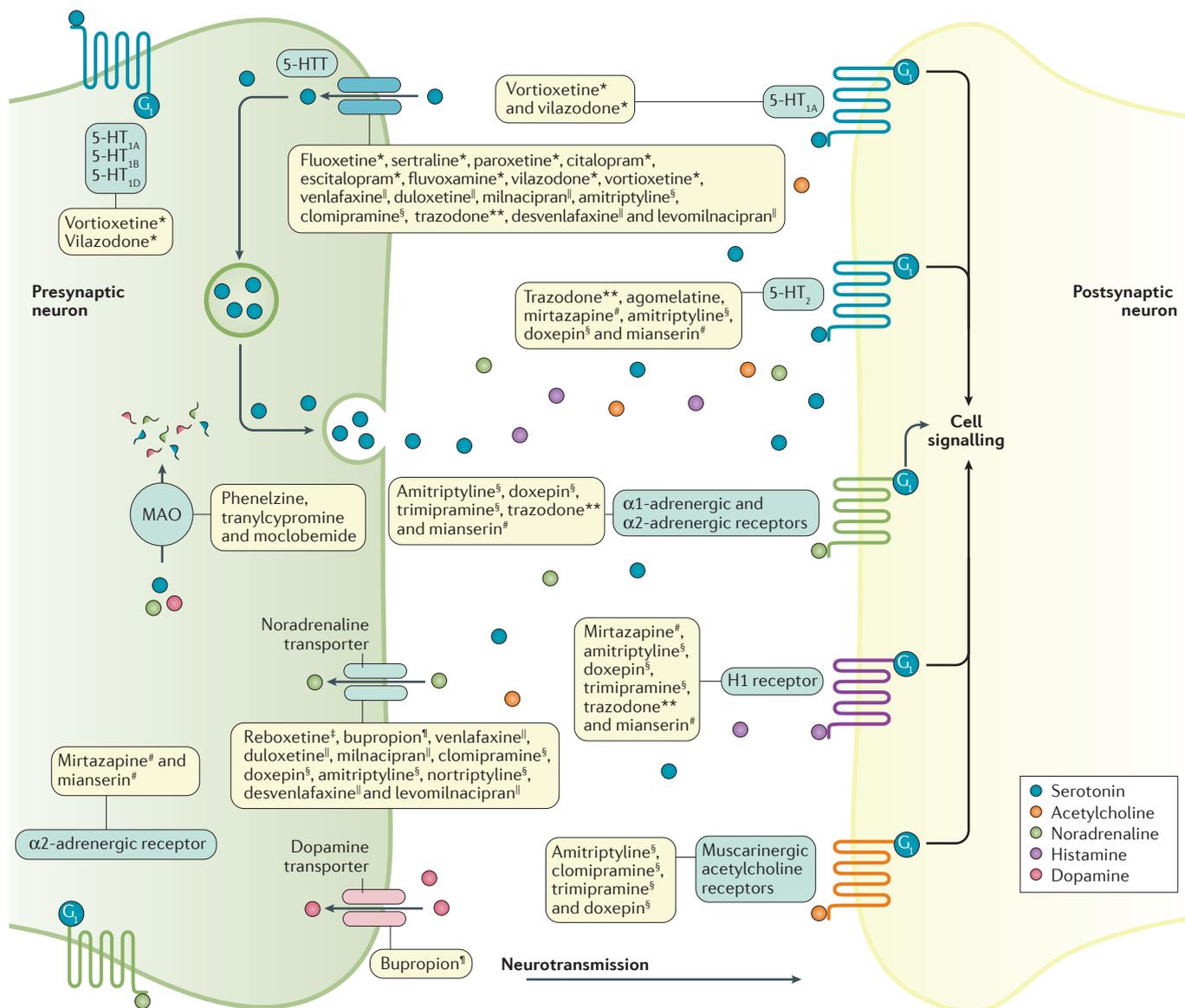

Figure 7 | **The mechanisms of action of antidepressant drugs.** The selective serotonin reuptake inhibitors (SSRIs; denoted with *) have been shown to have significant binding (antagonistic) to the serotonin transporter (5-HTT), thereby blocking serotonin reuptake. The relatively selective noradrenaline reuptake inhibitors (NRIs; denoted with ‡) have also shown at therapeutically relevant doses to have significant binding to the noradrenaline transporter. The tricyclic antidepressants (TCAs; denoted with §) and other cyclic antidepressants, as well as the serotonin–noradrenaline reuptake inhibitors (SNRIs; denoted with ‖), block the reuptake of serotonin and noradrenaline by binding to their transporter in varying ratios. TCAs, to varying degrees, are potent blockers of histamine H1 receptors, serotonin 5-HT$_2$ receptors, muscarinic acetylcholine receptors, and α1-adrenergic receptors. These effects account for the higher adverse-effect burden of the TCAs than the other classes of antidepressants. The noradrenaline–dopamine reuptake inhibitors (NDRIs; denoted with ¶) primarily block the reuptake of noradrenaline and dopamine. The α2-adrenergic receptor antagonists (denoted with #) seem to enhance the release of both serotonin and noradrenaline by blocking α2-autoreceptors. More-selective dual-action serotonin receptor antagonists/agonists primarily bind to serotonin 5-HT$_2$ receptors. Agomelatine is a melatonin receptor (MT1 and MT2) agonist (not shown) and a 5-HT$_{2C}$ antagonist without anticholinergic or antihistaminergic properties. Most currently used monoamine oxidase (MAO) inhibitors are irreversible inhibitors of both MAOA and MAOB, with dopamine, tyramine and tryptamine being substrates for both isoforms of MAO. Moclobemide is a selective and reversible MAOA inhibitor. In addition, other neurobiological systems (such as γ-aminobutyric acid, glutamate and opioids) are probably involved in the neurobiology of MDD and are to some extent targeted by more experimental antidepressive substances (such as ketamine). **Serotonin antagonist and reuptake inhibitor.

drugs, such as quetiapine or aripiprazole, is increasingly being used[168].

Finally, combination treatment generally refers to the prescribing of more than one antidepressant simultaneously. The array and number of combinatory possibilities have dramatically increased with the introduction of newer antidepressant agents. The two best-studied combination strategies, studied in STAR*D, are SSRIs or SNRIs combined with either bupropion (a noradrenaline–dopamine reuptake inhibitor) or mirtazapine (an α2-adrenergic receptor antagonist)[12].

Psychotherapy. In TRD, the most commonly used form of psychotherapy studied is cognitive–behavioural therapy (BOX 4). A systematic review of the pertinent literature concluded that the current evidence examining the effect of psychotherapy as augmentation or substitute therapy in TRD is sparse and shows mixed results[169]. However, the use of cognitive–behavioural therapy in citalopram non-responders in the STAR*D study was associated with comparable efficacy to pharmacotherapy[13]. Furthermore, a recent large-scale randomized controlled study showed both efficacy and long-term effectiveness of cognitive–behavioural therapy as adjunct to pharmacotherapy in TRD[170,171]. Finally, compared with treatment as usual, a meta-analysis showed efficacy for the cognitive–behavioural analysis system of psychotherapy, which is a specific psychotherapy for chronic depression including TRD[172].

ECT. In ECT, a seizure is elicited during short anaesthesia after the patient has provided informed consent. ECT is considered to be the most widely used and effective non-pharmacological biological treatment for TRD[173]. It is commonly used when a rapid antidepressant response is required, such as in very severely depressed and/or highly suicidal patients. The main tolerability issues of ECT are its adverse effects on cognition, especially anterograde and retrograde amnesia. Right unilateral ECT seems to be as effective as bilateral treatment, albeit bilateral treatment might lead to faster clinical response[173]. Another approach is to use ultra-brief pulse-width (UBP) stimulation to minimize cognitive adverse effects. However, a systematic review showed that UBP ECT might have lower efficacy and a slower speed of remission[174].

Emerging treatments. Newer treatments for TRD include numerous approaches, such as repetitive transcranial magnetic stimulation (rTMS), deep TMS (dTMS), magnetic seizure therapy (MST), transcranial direct current stimulation (tDCS), low-field magnetic stimulation (LFMS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), parenteral or intranasal ketamine and esketamine, as well as other pharmacological approaches.

Standard rTMS uses an eight-shaped coil to modulate neuronal activity to a maximum depth of 1.5–2.5 cm from the scalp. A recent review of 18 TRD studies of rTMS concluded that, for patients with MDD with at least two antidepressant treatment failures, rTMS is a reasonable, effective consideration[175]. However,

a meta-analysis has shown that rTMS is inferior to ECT with regard to efficacy in TRD[176].

In contrast to standard rTMS, dTMS modulates neuronal activity in deeper regions of the brain. One review concluded that dTMS in patients with TRD is effective both as a monotherapy and as an add-on treatment to pharmacotherapy[177].

MST combines elements of rTMS and ECT. In MST, an rTMS device is used to induce a seizure, but the procedure is otherwise carried out as ECT using a general anaesthetic and a muscle relaxant. A review of eight MST studies reported remission rates of 30–40% and no significant cognitive adverse effects[178].

tDCS typically applies a weak direct current via scalp electrodes overlying targeted cortical areas[179]. A recent review concluded that the data do not support the use of tDCS in TRD[180].

LFMS refers to a form of brain stimulation delivered in a magnetic field waveform inducing a low, pulsed electric field in the brain. Two sham-controlled pilot studies of LFMS have shown a rapid antidepressant effect in patients with a mood disorder, including patients with TRD[181].

VNS involves the surgical implantation of a pacemaker-like pulse generator in the chest, connected to a stimulating electrode attached to the vagus nerve in the neck. VNS results in the activation of various subcortical brain structures and the stimulation of hippocampal neurogenesis[182]. Despite the fact that the only controlled trial in TRD of VNS using a sham control did not achieve the pre-specified significance, and reported modest response rates in the acute phase, long-term, extension phases of VNS treatment have been associated with an increased therapeutic effect over time, with a sustained response rate of 40% and with a remission rate of 29% after a 9-month follow-up[182].

DBS involves the implantation of a pulse generator connected to two stimulating electrode wires, surgically placed in specific brain regions. DBS is typically reserved for patients with the most severe forms of TRD and requires further evaluation of administration methods and its role in MDD therapy[183].

A novel pharmacological approach to the treatment of TRD involves parenteral or intranasal administration of the glutamatergic drugs ketamine or esketamine, which are antagonists of N-methyl-D-aspartate (NMDA). A review of 21 studies showed that single ketamine intravenous infusions elicit a significant antidepressant effect from 4 hours to 7 days in patients with TRD[184]. Similar results were reported in a trial of a single intravenous infusion of esketamine[185]. Other drugs with NMDA receptor antagonistic properties have been associated with more-modest antidepressant effects than with ketamine; however, they have shown other potentially favourable characteristics, such as decreased dissociative or psychotomimetic effects. Other emerging pharmacological augmentation strategies use compounds such as S-adenosyl-methionine[186], L-methylfolate[187], omega-3 fatty acids[188], intravenous scopolamine[189] and the opioid modulator ALKS 5461 (REF. 190), but their efficacy is not well established yet.

Quality of life

Much of the burden of disease associated with MDD is related to its dramatic effect of on one's ability to work and the strain on family life. In a large survey carried out in the United States, MDD was associated with 27.2 workdays lost per affected worker per year[191]. Another aspect affected in MDD is cognition. Finally, MDD is a major risk factor for suicidal ideation and of suicide attempts, which can significantly reduce the quality of life of patients and their families.

Cognitive impairment

Considerable literature has described objectively measured cognitive deficits in patients with MDD. These deficits affect a wide range of cognitive domains including both 'hot' (emotion-laden) and 'cold' (non-emotional) cognition. One meta-analysis identified executive function, memory and attention as the pre-dominantly affected domains[192]. An attentional bias towards negative information has also been confirmed by meta-analysis[193]. Impairments in psychomotor speed, attention, visual learning and memory, as well as exec-utive function can be detected with small-to-medium effect sizes during a first episode of MDD[194].

Although the cognitive deficits are modest after remission (that is, in euthymic patients with MDD), slight impairments in executive control[192,195] and mem-ory[192] can remain, suggesting that cognitive deficits are not simply an epiphenomenon of decreased motivation during episodes of low mood. Cognitive impairment in MDD partly depends on the patient subgroup studied. MDD severity, for example, has been shown to be a strong predictor of cognitive dysfunction[196]. In addition, patients with psychotic depression have been shown to do significantly worse than patients with non-psychotic MDD on tests of verbal learning, visual learning and processing speed[197]. Neurocognitive impairment is a relevant factor in the quality of life of patients, as it is negatively associated with psychosocial functioning in MDD[198]. Overall, antidepressant pharmacotherapy seems to improve cognitive function[199].

Suicide risk

The most immediate clinical concern with MDD is its strong relation to suicidal intent and completed suicide[200]. Patients with MDD have a 1.8-fold incre-ased overall mortality and patients with MDD lose an estimated 10.6 life years in men and 7.2 years in women[7]. This is due, in part, to the increased risk of suicide in this population. In one analysis, the risk of suicide in MDD was almost 20-fold higher than in the general population[7].

The effectiveness of behavioural and psychosocial interventions to prevent suicide and suicide attempts has been supported by a recent meta-analysis, particu-larly for interventions that directly address suicidal thoughts[201]. Strategies to reduce suicides at 'suicide hotspots' (that is, public areas often used for suicides) by aiming to restrict access and to encourage help seek-ing might be effective, at least according to a recent meta-analysis[202].

Notably, meta-analyses of randomized controlled trials have not detected a beneficial effect of antidepres-sants to reduce suicide risk in MDD[203,204]. Importantly, the association between antidepressants use and suicidal-ity seems to be strongly age dependent[205,206]. Meta-analyses revealed that suicidal ideation or behaviour associated with antidepressants was nonsignificantly increased in patients <25 years of age, nonsignificantly decreased in patients 25–64 years of age and highly significantly decreased in patients >64 years of age. In any event, clinicians should pay special attention to suicidal ideation and suicidality in patients with MDD in general and during antidepressant pharmacotherapy[207].

Outlook

Given that MDD is prevalent worldwide, one of the highest priorities in the field should be to implement effective treatment in low-income countries in which <10% of patients with MDD receive adequate treat-ment[208,209]. The currently ongoing Mental Health Gap Action Programme (mhGAP)[210] of the WHO is aiming to scale-up services for mental disorders in countries with low and lower middle incomes.

In terms of the aetiology and pathophysiology of MDD, many questions remain unresolved. For example, how exactly is the immune system dysregu-lated in MDD? Are immunological alterations present in MDD in general or only in specific subtypes of the disease? Furthermore, there is a lack of replicated find-ings in both GWAS and G×E studies[37]. Thus, a crucial question remains how exactly environmental influences interact with the genome leading to MDD. In addition, how stable are epigenetic alterations of genomic read-out and are they reversible with successful therapy? An epi-demiological phenomenon consists in the repeatedly described sex differences in prevalence rates of MDD[2] and it will be important to examine the mechanisms that are responsible for the increased MDD prevalence in women. Finally, given the fact that MDD is a strong risk factor for developing metabolic and cardiovascu-lar diseases, and for a worse course and outcome in these diseases[5], it will be important to learn more about the mechanisms of association between MDD and other medical diseases, such as diabetes mellitus or coronary heart disease. Future research should also examine whether treatment of comorbid MDD reduces morbidity and mortality in medical patients.

A pivotal task in the future of MDD research will be to break down the heterogeneous clinical picture of MDD as a broad DSM-5 category into more narrowly defined disease entities with specific biologies. The initial goal of DSM-5 was to define psychiatric diagnoses by genetics, neuroimaging and other biological meas-ures. However, our knowledge has not yet sufficiently progressed to reliably base psychiatric diagnoses on biological measures. Nevertheless, the DSM still prov-ides clinicians and researchers with the opportunity to define subtypes of MDD by grouping patients according to distinct clinical characteristics (for example, melan-cholic versus atypical depression). Importantly, these subtypes have already been associated with different

neurobiological signatures[34]. Furthermore, the concepts of 'vascular depression' (REF. 211), 'metabolic depression' (REFS 212,213) or 'inflammatory depression' (REF. 214) that all imply a specific aetiology and potentially specific treatments warrant further validation.

Once valid MDD subtypes have been identified, specific treatments associated with better outcomes will hopefully follow. Several studies have predicted response to specific psychological or pharmacological treatment by clinical criteria such as history of childhood trauma[215], neuroimaging markers such as insula hypometabolism[216] or inflammatory markers such as C-reactive protein[217,218]. However, clinical subtypes (melancholic, atypical and anxious) could not predict treatment response in the iSPOT-D trial[219]. Ideally, so-called precision psychiatry will enable categorization of MDD subtypes as in the field of oncology, which has started to define different forms of cancer in the same organ into separate disease entities that require different treatment[220]. It remains to be seen whether the dimensional approach of the RDoC using concepts from genetics as well as from cognitive, affective and social neuroscience will achieve this goal. It has been argued that the RDoC approach disregards the distinction between 'sick' and 'well' and that the RDoC might introduce a gap between clinicians using DSM-5 and researchers using RDoC[221].

Better treatment for patients is the ultimate goal of all biomedical research and obviously this is true for MDD research as well. In terms of new psychotherapeutic approaches, the technological revolution with its fast evolving developments will enable technology-supported diagnostic and treatment options. This might include intervention tools that can detect and react to sensed states and behaviours, allowing just-in-time prompting and reinforcement of treatment congruent behaviours[144], as well as tools that can passively monitor risk of MDD.

Within pharmacological research, antidepressants that affect the glutamatergic system, such as ketamine, are currently under intense scientific scrutiny. A novel approach might be to use substances that stimulate neurogenesis in humans. The first (to our knowledge) phase Ib clinical study of the neurogenesis stimulator NSI-189 phosphate has been reported, showing efficacy compared with placebo in two out of four MDD outcome measures[156]. However, future studies are necessary to determine short-term and long-term safety and efficacy of substances that stimulate neurogenesis in patients.

MDD has considerable effects on the human condition and its aetiology and pathophysiology remain a complex puzzle. Consistent with Winston Churchill's famous quote "Success is not final, failure is not fatal: it is the courage to continue that counts", it will be worth every effort to relieve the enormous burden of MDD.

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PRIMER

Author contributions

Introduction (C.O.); Epidemiology (B.W.P.); Mechanisms/pathophysiology (C.O., S.M.G., B.W.P., C.M.P. and A.E.); Diagnosis, screening and prevention (A.F.S.); Management (M.F. and D.C.M.); Quality of life (S.M.G.); Outlook (C.O. and A.F.S.); Overview of the Primer (C.O.).

Competing interests

C.O. has received honoraria for lectures from Lundbeck and Servier and for membership in a scientific advisory board from Lundbeck and Neuraxpharm. S.M.G. has received honoraria from Novartis and travel reimbursements from Novartis, Merck Serono and Biogen Idec and has received in-kind research support for conducting clinical trials from GAIA AG, a commercial developer and vendor of health care management and eHealth interventions. B.W.P. has received research funding from Jansen Research and is supported by a VICI grant from the Dutch Scientific Organization. C.M.P. was supported by the National Institute for Health Research Mental Health Biomedical Research Centre in Mental Health at South London, Maudsley NHS Foundation Trust and King's College London, the grants 'Persistent fatigue induced by interferon-α: A New Immunological Model for Chronic Fatigue Syndrome' (MR/J002739/1), and 'Immuno-psychiatry: a consortium to test the opportunity for immunotherapeutics in psychiatry' (MR/L014815/1) from the Medical Research Council (UK), research funding from the Medical Research Council (UK) and the Wellcome Trust for research on depression and inflammation as part of two large consortia that also include Johnson & Johnson, GSK, Lundbeck and Pfizer, and research funding from Johnson & Johnson as part of a programme of research on depression and inflammation. In addition, C.M.P. has received a speaker's fee from Lundbeck. A.E. has received research funding from Brain Resource, Inc. and honoraria for consulting from Otsuka, Acadia and Takeda. M.F. reports the following research support: Abbot Laboratories; Alkermes, Inc.; American Cyanamid; Aspect Medical Systems; AstraZeneca; Avanir Pharmaceuticals; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon; Cerecor; Clintara, LLC; Covance; Covidien; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; FORUM Pharmaceuticals; Ganeden Biotech, Inc.; GlaxoSmithKline; Harvard Clinical Research Institute; Hoffman-LaRoche; Icon Clinical Research; i3 Innovus/Ingenix; Janssen R&D, LLC; Jed Foundation; Johnson & Johnson Pharmaceutical Research & Development; Lichtwer Pharma GmbH; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante; Methylation Sciences Inc.; National Alliance for Research on Schizophrenia & Depression (NARSAD); National Center for Complementary and Alternative Medicine (NCCAM); National Coordinating Center for Integrated Medicine (NiiCM); National Institute of Drug Abuse (NIDA); National Institute of Mental Health (NIMH); Neuralstem, Inc.; Novartis AG; Organon Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; Pharmacia-Upjohn; Pharmaceutical Research Associates., Inc.; Pharmavite® LLC; PharmoRx Therapeutics; Photothera; Reckitt Benckiser; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Sanofi-Aventis US LLC; Shire; Solvay Pharmaceuticals, Inc.; Stanley Medical Research Institute (SMRI); Synthelabo; Takeda Pharmaceuticals; Tal Medical; Wyeth-Ayerst Laboratories; Advisory Board/ Consultant: Abbott Laboratories; Acadia; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; Auspex Pharmaceuticals; Avanir Pharmaceuticals; AXSOME Therapeutics; Bayer AG; Best Practice Project Management, Inc.; Biogen and BioMarin Phar. D.C.M. has received honoraria for lectures and for membership in a scientific advisory board from Otsuka. A.F.S. has, since 2015, served as a consultant for Alkermes, Cervel, Clintara, Forum Pharmaceuticals, McKinsey and Company, Myriad Genetics, Neurontics, Naurex, One Carbon, Pfizer, Takeda, Sunovion and X-Hale and as a speaker for Pfizer; he holds equity in Amnestix, Cervel, Corcept (co-founder), Delpor, Gilead Incyte, Merck, Neurocrine, Seattle Genetics, Titan and X-Hale; and he is listed as an inventor on pharmacogenetic and antiglucocorticoid use patents on prediction of antidepressant response.

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