Depression

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Major depression is a common illness that severely limits psychosocial functioning and diminishes quality of life. In 2008, WHO ranked major depression as the third cause of burden of disease worldwide and projected that the disease will rank first by 2030.[1] In practice, its detection, diagnosis, and management often pose challenges for clinicians because of its various presentations, unpredictable course and prognosis, and variable response to treatment.

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Epidemiology

Prevalence

The 12-month prevalence of major depressive disorder varies considerably across countries but is approximately 6%, overall.[2] The lifetime risk of depression is three times higher (15–18%),[3] meaning major depressive disorder is common, with almost one in five people experiencing one episode at some point in their lifetime. Hence, in primary care, one in ten patients, on average, presents with depressive symptoms,[4] although the prevalence of depression increases in secondary care settings. Notably, the 12-month prevalence of major depressive disorder is similar when comparing high-income countries (5·5%) with low-income and middle-income countries (5·9%), indicating that major depressive disorder is neither a simple consequence of modern day lifestyle in developed countries, nor poverty.[5,6] Furthermore, although social and cultural factors,[7] such as socioeconomic status, can have a role in major depression, genomic and other underlying biological factors ultimately drive the occurrence of this condition.[8] The most probable period for the onset of the first episode of major depression extends from mid-adolescence to mid-40s, but almost 40% experience their first episode of depression before age 20 years, with an average age of onset in the mid-20s (median 25 years [18–43]).[9,10] Across the lifespan, depression is almost twice as common in women than in men and, in both genders, a peak in prevalence occurs in the second and third decades of life, with a subsequent, more modest peak, in the fifth and sixth decades.[2,11–13] The difference in prevalence of depression between men and women is referred to as the gender gap in depression and is thought to be linked to sex differences in susceptibility (biological and psychological), and environmental factors that operate on both the microlevel and macrolevel.[14]

Course and prognosis

The onset of depression is usually gradual, but it can be abrupt sometimes, and depression's course throughout life varies considerably. For most patients, the course of illness is episodic, and they feel well between acute depressive episodes. However, the illness is inherently unpredictable and, therefore, the duration of episodes, the number of episodes over a lifetime, and the pattern in which they occur are variable. Major depressive disorder is a recurrent lifelong illness and so recovery is somewhat of a misnomer. In practice, the term is used to describe patients that are no longer symptomatic and have regained their usual function following an episode of major depression. With treatment, episodes last about 3–6 months, and most patients recover within 12 months.[15] Long-term stable recovery is more probable in community settings and among those patients seen by general physicians than in hospital settings.[16] Longer-term (2–6 years), the proportion of people who recover is much less, dropping to approximately 60% at 2 years, 40% at 4 years, and 30% at 6 years with comorbid anxiety having a key role in limiting recovery.[17] The likelihood of recurrence is high, the risk increases with every episode, and, overall, almost 80% of patients experience at least one further episode in their lifetime.[18,19] The probability of recurrence increases with each episode and the outcome is less favourable with older age of onset.[20] Furthermore, although more than half of those affected by a major depressive episode recover within 6 months, and nearly three-quarters within a year, a substantial proportion (up to 27%) of patients do not recover and go on to develop a chronic depressive illness, depending upon baseline patient characteristics and the setting within which they are managed.[21,22]

Diagnosis

The two main classificatory diagnostic systems (Diagnostic and Statistical Manual of Mental Disorders [DSM],[23]

Search strategy and selection criteria

We searched PubMed for studies published between Jan 1, 2010, and Jan 1, 2018, with the terms "depression", "depressive disorder", and "depressive disorder, major", with specifiers "therapy" and "drug therapy", as well as "antidepressive agents" and "psychotherapy". The search excluded articles on depression in the context of bipolar disorder, other psychiatric illnesses (such as schizophrenia), and medical illnesses. We restricted the search to English language publications and focused on publications from the past 5 years. We referred to older publications in the field, especially those regarded as seminal and those that have been highly cited. The search was updated in the periods March 12–16, 2018, and then again July 2–7, 2018, and the bibliographies of selected articles were also reviewed to retrieve publications deemed to be relevant to this Seminar.
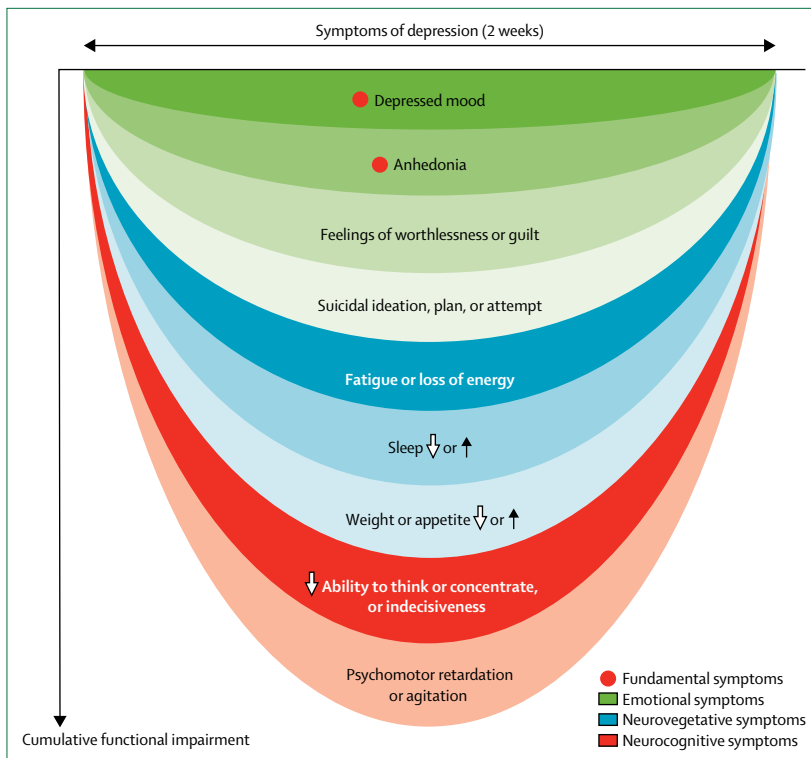

Figure 1: Defining major depressive disorder

Key symptoms of Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 for major depressive disorder. For a diagnosis of major depressive disorder, the individual needs to present with five or more of any of the symptoms nearly every day during the same 2-week period, provided at least one of these symptoms is a fundamental one. The clinical symptoms of major depressive disorder are usually accompanied by functional impairment. The greater the number and severity of symptoms (as opposed to particular symptoms), the greater the probability of the functional impairment they are likely to confer. The symptoms of depression can be grouped into emotional, neurovegetative, and neurocognitive domains. Importantly sleep, weight, and appetite are usually diminished in depression but can also be increased, and suicidal ideation, plans, or an attempt should be documented whenever depression is suspected.

identify depression in various clinical settings, and some that rely on self-report can be used in a waiting room or online.[26] However, several screening limitations need to be considered. One limitation is the absence of hierarchy among the range of symptoms that span several domains (emotional, cognitive, and neurovegetative), and which symptoms, if any, warrant priority or greater weighting is unclear. The only symptoms given some primacy are those nominated as fundamental, whereas the remainder carry equal significance (figure 1). In practice, this absence of prioritisation means that very different clinical presentations can qualify as having a depressive syndrome of seemingly equivalent severity, even though the clinical significance of the different presentations can vary markedly.[27]

In DSM-5, major depressive disorders are separated from bipolar disorders, with the key distinction that manic symptoms only occur in bipolar disorders.[28] Major depressive disorder is the principal form of depression and is characterised by recurrent depressive episodes. The diagnosis can be made after a single episode of depression that has lasted two weeks or longer. If episodes of depression do not resolve and last for extended periods of time, this pattern is described as chronic depression. If depressive symptoms are present (on most days) for at least 2 years without any periods of remission exceeding 2 months, the condition is termed persistent depressive disorder or dysthymia.

It is crucial to note that major depressive disorder is different from unhappiness or typical feelings of sadness. To qualify as major depression, an individual must present with five or more specified symptoms (figure 1) nearly every day during a 2-week period, and the symptoms are clearly different from the individual's previous general functioning. Furthermore, for the diagnosis of a depressive episode, depressed mood or anhedonia must be present.[23] When depressive symptoms are present but are insufficient in number or severity to be regarded as a syndrome, they are sometimes referred to as subthreshold depressive symptoms. These are important as they could serve as early indicators of a major depressive episode.

The symptoms of depression can be broadly grouped into emotional, neurovegetative, and cognitive symptoms, but because they also commonly occur in other psychiatric disorders and medical diseases, detection of a depressive syndrome can be difficult. Some depressive symptoms, such as diminished concentration and psychomotor agitation, are similar to those of mania, and so, when formulating a diagnosis of depression, the possibility of an emerging bipolar disorder warrants consideration.[29,30] At the same time, it is important to ensure that the symptoms of depression cannot be explained by an alternative psychiatric diagnosis, such as an anxiety disorder, schizophrenia, or a medical illness, or the side-effects of a medication. Anxiety is

and International Classification of Diseases [ICD][24]) rely on the identification of a number of key symptoms (figure 1). Notably, none of the symptoms are pathognomonic of depression, and do feature in other psychiatric and medical illnesses. Therefore, the definition of depression as a disorder is based on symptoms forming a syndrome and causing functional impairment. Some symptoms are more specific to a depressive disorder, such as anhedonia (diminished ability to experience pleasure); diurnal variation (ie, symptoms of depression are worse during certain periods of waking hours); and intensified guilt about being ill. Other symptoms, such as neurovegetative symptoms, including fatigue, loss of appetite or weight, and insomnia, are very common in other medical illnesses.[25]

Both taxonomies, DSM and ICD, are widely used to diagnose major depressive disorder within hospital, outpatient, and community settings, but for research, DSM is the predominant classificatory system. In addition to DSM and ICD checklists, the severity of major depression can be quantified with rating scales. Therefore, screening tools have been developed to help

common in the context of depression, and almost two-thirds of individuals with major depressive disorder have clinical anxiety.[31] Anxiety symptoms often appear 1 year or 2 years ahead of the onset of major depression,[32] and with increasing age, become a more pronounced feature of major depressive episodes. Therefore, anxiety can manifest both as comorbidity and as a predominant feature of major depressive disorder, sometimes termed anxious depression and described in DSM-5 as an anxious distress specifier (figure 2).[33] Of note, depressive symptoms overlap considerably with those of bereavement,[34] but if the symptoms of depression are severe and persist well beyond the acute grieving period, then consideration should be given to a separate diagnosis of major depressive disorder.[35] Alternatively, a diagnosis of adjustment disorder should be considered when the symptoms do not represent typical bereavement but have arisen in response to an identifiable stressor (within 3 months of the onset of the stressor), or the symptoms produce disproportionately marked distress that results in functional impairment but do not meet the criteria of a major depressive episode. This diagnosis can occur with either depressed mood, anxiety, or both.[23] Importantly, stressors are common in both major depressive disorder and adjustment disorder, and therefore stressors are not useful for distinguishing these diagnoses. The key differences are severity and diagnostic criteria of a major depressive episode.

Specifiers and subtypes

In practice, it is useful to define the character of each depressive episode, particularly the current or most recent period of illness. This definition is achieved by use of specifiers, which define the pattern of illness, its clinical features (both signs and symptoms), severity, time of onset, and whether it has remitted (figure 2).[4,35,36] Some of the clinical features generate putative subtypes of major depressive disorder. For example, the specifier with melancholic features—ie, a diminished reactivity of affect and mood, a pervasive and distinct quality of depressed mood that is worse in the morning, along with anhedonia, guilt, and psychomotor disturbance—denotes a melancholic subtype. Such subtyping is sometimes helpful and it might have potential treatment implications.[37] Melancholia is generally more responsive to pharmacotherapy and electroconvulsive therapy. Similarly, major depressive disorder with psychotic features (psychotic depression) often responds best to electroconvulsive therapy, especially when the psychotic features are mood-congruent—ie, feature depressive themes concerning death, loss, illness, and punishment.[38,39] Sometimes, alongside psychotic features, patients can have marked psychomotor disturbance[40] and other symptoms that reflect catatonia.[41] These subtypes of major depressive disorder are uncommon and most presentations of depression in the community involve symptoms of anxiety,[42] described as anxious distress.[43] Such presentations are less responsive to antidepressants, even though antidepressants are often used to treat anxiety disorders, suggesting that admixtures of anxiety and depressive symptoms probably reflect additional underlying psychological factors, such as those pertaining to an individual's personality. Characterising depression in this manner is often helpful, and the use of specifiers to describe depressive episodes in greater detail is good practice that should be routine and adopted more widely.

Detection and screening

Depression can manifest in many forms with different combinations of symptoms, which makes its detection more difficult, especially in the context of other illnesses. This mix of symptoms could also explain why depression is often missed or misdiagnosed in primary
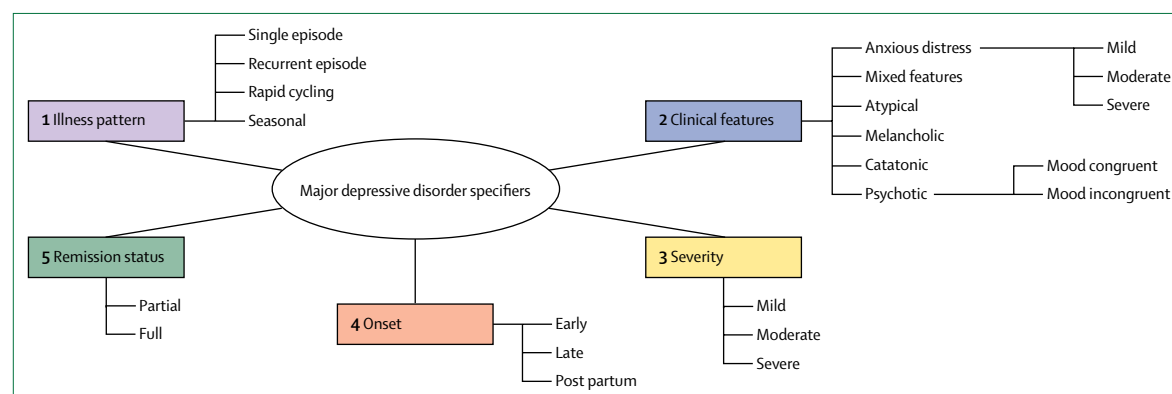

Figure 2: **Major depressive disorder specifiers**
Episodes of major depression can be described in greater depth by specifiers (outlined in Diagnostic and Statistical Manual of Mental Disorders-5) that provide additional information regarding the pattern of the illness and its clinical features. Specifiers can also indicate the severity of the episode, when it first emerged (onset), and whether it has remitted (status). For example, in clinical practice, a typical episode of depression can be described as suffering from a recurrence of depression that is moderately severe with melancholic features and has partly remitted in response to initial treatment.

care.[27] Greater awareness of depression increases its successful diagnosis, but screening for depressive illness at a population level has been problematic, which makes its overall detection and diagnosis more difficult.[26,44] A substantial proportion of depression probably goes undetected and undiagnosed, and hence published statistics do not fully reflect the burden of the illness. The reasons for this lack of detection are complex and vary across cultures and different health systems, and alongside failures in detection and diagnosis, stigma is an important factor that has been difficult to quantify.[45] Case-finding tools that can be used to identify depression are popular among clinicians, such as the nine-item Patient Health Questionnaire (PHQ-9), which comes in three forms, all of which are brief and generally acceptable to patients.[46] Such tools can usefully guide detection and the assessment of severity, but it is important that clinicians also assess contextual factors and general functioning, and do not rely solely on questionnaires. Given the prevalence of depression in primary care, routinely asking all patients about mood, interest, and anhedonia since the last visit is essential,[47] and when more detailed screening is needed, the burden of administering questionnaires can be limited by the use of computerised adaptive testing methods.[48] In addition to enhancing detection through screening, the diagnosis and treatment of major depression can be improved through educational programmes that have great effect on suicide prevention methods.[49] However, as shown by a study in Gotland, Sweden, the turnover of doctors due to a 2-year term of service contributed to the requirement for a refresher programme on depression.[50] Moreover, attrition in knowledge occurs because once no longer engaged in an educational programme, the general practitioner's attention shifts to other medical conditions. Therefore, sustaining change in practice requires ongoing education.

Pathology

Understanding of the pathophysiology of major depressive disorder has progressed considerably, but no single model or mechanism can satisfactorily explain all aspects of the disease. Different causes or pathophysiology might underlie episodes in different patients, or even different episodes in the same patient at different times. Psychosocial stressors and biological stressors (eg, post-partum period) can result in different pathogenesis and respond preferentially to different interventions. Investigations into the neurobiology of depression have also involved extensive animal research, but extrapolation from animal models of depression and the translation of findings from basic science into clinical practice has proven difficult.[51] Therefore, to understand the pathophysiology of major depressive disorder, focusing on mechanisms informed directly by clinical studies and examining both

biological and psychosocial factors can be more useful, noting that contributions from these factors are variable.

The monoamine hypothesis

The observation, in mid-20th century, that the anti-hypertensive reserpine could trigger major depression and reduce the amount of monoamines, caused interest in the potential role of monoamine neurotransmitters (serotonin, noradrenaline, and dopamine) in the pathogenesis of major depressive disorder. The monoamine theory of major depressive disorder was supported by findings that tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) enhanced monoamine neurotransmission by different mechanisms, suggesting that this theory explained how antidepressants work (appendix).[52] This model has endured, partly because of ongoing corroborative findings from studies that have examined the neurotransmitters and their metabolites, both in vivo and post mortem. The model also endured because other, more selective medications, such as autoreceptor antagonists (eg, mirtazapine for the adrenergic system) and serotonin agonists (eg, gepirone), are clinically effective antidepressants.[53] However, this model does not explain the notable variability in the clinical presentation of major depressive episodes, even within the same patient, and why some patients respond to one type of antidepressant and others do not. Importantly, this model does not explain why antidepressants take weeks to work.[54]

Hypothalamic–pituitary–adrenal axis changes

The hypothalamic–pituitary–adrenal (HPA) axis has been the focus of depression research for many decades.[55–57] One of the most consistent biological findings in more severe depression with melancholic features, and associated with changes in the HPA axis, is the increased amount of plasma cortisol. This biological difference is due to a combination of excessive stress-related cortisol release and impaired glucocorticoid receptor-mediated feedback inhibition. Notably, HPA axis changes are also associated with impaired cognitive function,[58] and a failure of HPA axis normalisation with treatment is associated with poor clinical response and high relapse.[59] Despite these insights, successful translation of this knowledge into clinically effective treatments has not occurred, and treatments that modify HPA axis function, such as glucocorticoid receptor antagonists, have not worked in clinical trials.[60–62]

Inflammation

Peripheral cytokine concentrations have been linked to brain function, wellbeing, and cognition.[63] Peripheral cytokines can act directly on neurons and supporting cells, such as astrocytes and microglia, after traversing the blood–brain barrier, or via signals mediated by

afferent pathways, such as those in the vagus nerve.[64] These mechanisms could explain why individuals with autoimmune diseases and severe infections are more likely to have depression, and why cytokines administered therapeutically, such as interferon gamma and interleukin 2, trigger depression. The role of inflammation in the causation and exacerbation of depression is further supported by the finding that increased amount of interleukin 6 in childhood enhances the risk of developing depression later in life, and by the evidence of microglial activation and neuroinflammation found in the brains of patients with depression examined post mortem.[65] These insights have prompted the examination of non-steroidal anti-inflammatory drugs in the treatment of major depressive disorder.[66]

Neuroplasticity and neurogenesis

One of the most important discoveries in this century has been the identification, in the adult brain, of pluripotent stem cells from which new neurons can be generated, a process termed neurogenesis (appendix). The growth and adaptability at a neuronal level has been more broadly termed neuroplasticity, and it is possibly this neuroplasticity at a cellular level that is altered by inflammation and HPA axis dysfunction, both caused by environmental stress.[67] The process of neurogenesis is controlled by regulatory proteins, such as brain-derived neurotrophic factor (BDNF), which is diminished in patients with major depressive disorder. Even more important, perhaps, is the fact that reduced amounts of BDNF in people with depression can be restored with antidepressant therapies, either pharma-cotherapy or psychological interventions.[68] In animal studies, limiting neurogenesis prevents antidepressant action and has been shown to result in depression-like symptoms, especially in stressful situations. Therefore, neurogenesis has been suggested to facilitate resilience against stress, which could be the basis of antidepressant clinical effects.[69] Post-mortem studies of patients with depression show a deficit of granule neurons in the dentate gyrus of untreated individuals, compared with non-depressed and treated groups. Patients treated for depression have substantially more dividing neuronal progenitor cells compared with an untreated depression group, and even compared with a non-depressed group.[70] These findings are consistent with mouse studies showing that anti-depressants can work by increasing neurogenesis in the adult brain.

Structural and functional brain changes

Advances in technology and computing over the past quarter of a century have had an immense impact on our understanding of brain structure and function, but meaningful insights have only begun to emerge in the past decade, as it became possible to scan larger numbers of patients and reliably combine neuroimaging data.

Structural studies in patients with depression have consistently found that hippocampal volume is smaller in major depression compared with people without depression,[71] and some studies have related the degree of volume loss to duration of untreated lifetime depres-sion.[72,73] Post-mortem studies have shown that dentate gyrus volume in untreated patients with depression is about half of that of both a non-depressed comparison group and a group of patients with depression who received treatment.[74,75] Whether the smaller hippocampus can be reversed with treatment, and whether it is required for an antidepressant response, is yet to be shown in clinical studies.

Functional neuroimaging provides information about brain networks involved in key processes, such as emotion regulation, rumination, impaired reward pathways related to anhedonia, and self-awareness. Studies examining these networks in depressive disorders have found that, generally, the amygdala has increased activity and connectivity, and other structures, such as the subgenual anterior cingulate, are hyperactive, but that the insula and dorsal lateral prefrontal cortex are hypoactive, in individuals with depression.[76,77] However, the brain changes that have been identified in major depression are related to a highly heterogeneous clinical presentation and, therefore, are also highly variable, making it difficult to replicate results from study to study.[78–80] Different types of treatment, such as medication, psychotherapies, and stimulation therapies, have different effects, and research linking pre-existing brain abnormalities to choice of optimal treatment is an area of current research.

Genes

Twin and adoption studies have shown that major depressive disorder is moderately heritable.[81] First degree relatives of patients with major depression have a three times increase in their risk of developing major depressive disorder compared with those who do not have first degree relatives with a diagnosis of major depression. Unfortunately, reliable identification of the genes responsible has proven difficult. So far, genome-wide association studies (GWAS) have identified multiple genes, each with a small effect, and until 2018, few gene hits had been replicated.[82] However, current GWAS have begun to successfully identify risk variants and have shown replicable findings that might begin to inform the pathophysiology of major depressive disorder.[82–84] Studies that have examined more homo-geneous cases with severe illness also appear promising and have identified loci contributing to risk of major depressive disorder.[85] Given the variability of findings, in addition to genomic investigations, epigenetic factors are now being examined.

Environmental milieu

The potential role of life events in precipitating and possibly causing major depressive disorder has long

been recognised.[86,87] For example, early studies examined the impact of stressful life events closely juxtaposed to episodes of major depression, such as preceding its onset by up to a year.[88,89] These stressful life events in adults include life threatening or chronic illness, financial difficulties, loss of employment, separation, bereavement, and being subjected to violence. The associations between stressful life events and depression have been found to be robust,[90,91] though a subgroup of patients seems vulnerable to the effects of stressful life events and another group seems relatively resilient, possibly reflecting biological predispositions. A second approach has examined childhood factors, such as maltreatment including abuse, loss, and neglect, that appear to be associated with a vulnerability to develop major depression during adulthood when confronted with stressful life events.[92] By stratifying adversity, such studies have identified at least two types of molecular variants that predispose individuals to major depressive disorder: molecules whose effects depend on adversity and molecules whose effects are present in all cases, irrespective of adversity.[93] These studies have identified both pure epigenetic mechanisms and gene-environment interactions. Animal and clinical studies have linked early childhood trauma to later life depression via changes in the HPA axis, particularly glucocorticoid receptor hypofunction (appendix).[61] Specifically, early exposure to childhood adversity results in DNA methylation of key sites in the glucocorticoid receptor gene, reducing its expression.[94] Thus, exposure to emotional neglect, or sexual and physical abuse, has an effect on the likelihood, severity, and chronicity of major depression (appendix).[86,95]

Epigenetics (gene-environment interactions)
In the past decade, an exciting discovery is that the environment can directly impact the interpretation of genetic information, and that some genes are activated by environmental factors. This process has been described as the gene-environment interaction and it is determined by epigenetic mechanisms (appendix).[96] Research examining this phenomenon has uncovered potentially new pathways and mechanisms by which environmental factors might have a role in the modification of brain neurobiology, altering, for example, neuronal plasticity.[97,98] However, this new field faces considerable challenges, and although these discoveries are exciting and have stimulated further research in genetics, studies developing therapeutic approaches that can modify pathogenic epigenetic effects are needed before the potential exists for clinical interventions to build on these observations.[93,99]

Management of major depressive disorder
When treating a depressive episode, the initial objective is the complete remission of depressive symptoms and broadly speaking, this objective can usually be achieved by use of psychological therapy, pharmacotherapy, or both.[100–102] However, before embarking on a specific treatment pathway, it is important to stop the administration of drugs that can potentially lower mood, address any substance misuse, and, when possible, use general measures such as sleep hygiene, regular exercise, and healthy diet.[4,35] For mild cases of major depressive disorder, psychological treatment alone can suffice and an evidence-based psychotherapy, such as cognitive behavioural therapy, should be offered first. This therapy can also be used to treat depression of moderate severity, but in most cases medication is likely to be needed, and a combination of pharmacotherapy and psychological treatment is preferable. In cases of severe major depressive disorder, medication should be considered as first-line treatment, and electroconvulsive therapy is an option for those patients who do not respond to medication.

Psychological therapies
Several psychotherapies are available for major depressive disorder.[35,101,102] The most popular and effective psychotherapies are shown in figure 3. Each style of therapy draws on different conceptual designs which
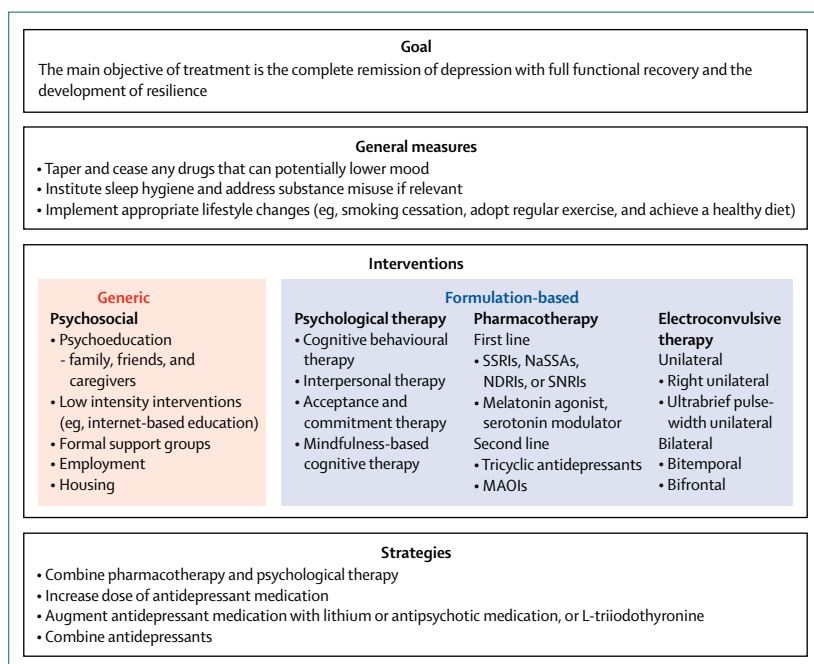

Goal

The main objective of treatment is the complete remission of depression with full functional recovery and the development of resilience

General measures

• Taper and cease any drugs that can potentially lower mood
• Institute sleep hygiene and address substance misuse if relevant
• Implement appropriate lifestyle changes (eg, smoking cessation, adopt regular exercise, and achieve a healthy diet)

Interventions

Generic	Formulation-based		
Psychosocial	**Psychological therapy**	**Pharmacotherapy**	**Electroconvulsive therapy**
• Psychoeducation - family, friends, and caregivers	• Cognitive behavioural therapy	First line • SSRIs, NaSSAs, NDRIs, or SNRIs	Unilateral • Right unilateral
• Low intensity interventions (eg, internet-based education)	• Interpersonal therapy • Acceptance and commitment therapy	• Melatonin agonist, serotonin modulator	• Ultrabrief pulse-width unilateral
• Formal support groups	• Mindfulness-based cognitive therapy	Second line • Tricyclic antidepressants	Bilateral • Bitemporal
• Employment • Housing		• MAOIs	• Bifrontal

Strategies

• Combine pharmacotherapy and psychological therapy
• Increase dose of antidepressant medication
• Augment antidepressant medication with lithium or antipsychotic medication, or L-triiodothyronine
• Combine antidepressants

Figure 3: **Management of major depressive disorder**
General measures: before instituting any intervention, factors that can worsen depression and general measures that can improve mood and make management less complicated, such as exercise and withdrawal of medications and substances known to exacerbate depression, should be reviewed and instituted when necessary. Interventions: four broad categories of interventions can be used to treat major depressive disorder—generic psychosocial interventions, formulation-based interventions of psychological therapy, pharmacotherapy, and electroconvulsive therapy. Strategies: in instances where treatments are ineffective or only partially effective, several strategies can be employed, combining different types of treatment or making individual treatments more effective. SSRIs=selective serotonin reuptake inhibitors. NaSSAs=noradrenergic and specific serotonergic antidepressant. NDRIs=norepinephrine-dopamine reuptake inhibitors. SNRIs=serotonin-norepinephrine reuptake inhibitors. MAOIs=monoamine oxidase inhibitors.

are used to build a framework of treatment, and each therapy has slightly different targets in mind.[103,104] Cognitive behavioural therapy is the most widely available and best tested psychotherapy, which teaches patients with major depressive disorder how to identify negative patterns of thinking that contribute to their depressed feelings. This type of psychotherapy provides techniques on how to address these negative thoughts and, when possible, replace them with healthier, positive ideas.[105] Interpersonal therapy differs from cognitive behavioural therapy, because it focuses predominantly on difficulties within relationships, particularly interpersonal conflict and problems in social interactions.[106] Overall, psychotherapies are effective in treating major depressive disorder, but it has been difficult to show differences between them.[107] The reason for this difficulty, according to one viewpoint prevalent in this field of study, is that the elements that determine therapeutic benefit are common to all psychotherapies and, therefore, distinguishing the therapies in terms of treatment effect is not possible. These common elements are related to the therapist and the therapeutic relationship, and involve components such as warmth, positive regard, and a genuine sense of care.[108]

An alternative view is that each of the psychotherapies has specific, and somewhat unique, therapeutic factors, and that they affect change via distinct pathways.[109] Therefore, this idea argues that to determine differences between therapies, far more sophisticated tools and much larger studies than those that have been done are needed. In patients with mild to moderate depression, psychotherapies seem to be as effective as pharmacotherapy. This effectiveness is not present in severe depression, because patients are too ill to engage with psychotherapy.[110] The longer-term effects of some psychotherapies, such as cognitive behavioural therapy, have also been shown to persist for a year or more after treatment, whereas antidepressant medication only works while it is being taken. The preference expressed by patients for psychological interventions, their effectiveness in combination with antidepressants, and their comparative efficacy and safety in relation to medications suggest that combination of the treatment methods might be the optimal strategy for managing major depressive disorder.[111] Outcomes could be further enhanced as greater understanding of the mechanisms of psychological treatments is achieved and models are developed that provide greater explanatory specificity.[112] However, in practice, the main limitations of psychotherapy are lack of availability because very few trained therapists are available and treatment is expensive.[113] To overcome these issues, alternative methods for treatment delivery have been explored, such as providing psychotherapy to groups of patients at a time, or individually, but over the telephone or via the internet.[114,115]

Pharmacotherapy
The pharmacotherapy for major depressive disorder has been founded on enhancement of monoaminergic neurotransmission.[116] But newer antidepressants target other brain systems, like the N-methyl-D-aspartate (NMDA) receptor, melatonin, or gamma-aminobutyric acid (appendix).
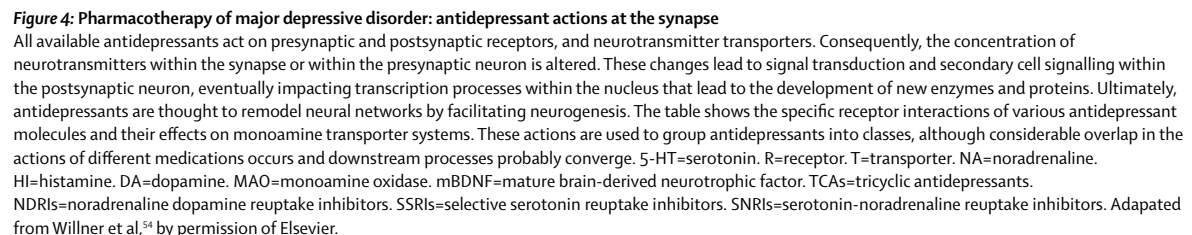
Antidepressant actions
The precise mechanisms by which antidepressants improve mood remains unknown, but most antidepressants acting on monoaminergic neurotransmission produce initial effects within the synapse, which then impact intracellular signalling and second messenger pathways.[54] These pathways culminate in changes in gene expression, neurogenesis, and synaptic plasticity, and, ultimately, these adaptive changes lead to therapeutic benefit.[117] The pharmacological effects of antidepressants are diverse and complicated, and the grouping of antidepressants into classes based on their principal pharmacological action is overly simplistic, but it remains useful in practice, when the clinical effects of antidepressants are broad and overlapping (figure 4).

Effectiveness of antidepressants
Trials examining the potency of antidepressant drugs have traditionally focused on efficacy, and in clinical contexts have usually assessed this potency somewhat crudely, seeking a 50% reduction in symptoms.[35] Some of the earliest developed antidepressants, such as the tricyclics and MAOIs, remain among the most efficacious drugs available, but are in minimal use today.[118] In most settings, and in particular when first commencing treatment, these medications have been displaced by newer drugs with more pharmacologically selective actions and, consequently, fewer side-effects.[119] Therefore, over the last quarter of a century, the selective serotonin reuptake inhibitors (SSRIs) have become the first-line antidepressant medication class, despite only moderate efficacy that can take weeks to produce a measurable benefit (figure 3). Furthermore, SSRIs can also produce significant side-effects that patients do not tolerate, including sexual dysfunction, weight gain, nausea, and headaches.[120]

In a network meta-analysis that compared efficacy and acceptability of antidepressant medications in the acute treatment of major depressive disorder,[121] all 21 medications, which included the two WHO recommended essential antidepressants, amitriptyline and clomipramine, showed greater efficacy than placebo, with amitriptyline and some of the dual-acting drugs (eg, mirtazapine, duloxetine, and venlafaxine) at the top of the list. In terms of acceptability, only agomelatine and fluoxetine were more tolerable than placebo, whereas most antidepressants were on par, except clomipramine, which was more poorly tolerated than placebo. The study also assessed head-to-head

Figure 4: **Pharmacotherapy of major depressive disorder: antidepressant actions at the synapse**
All available antidepressants act on presynaptic and postsynaptic receptors, and neurotransmitter transporters. Consequently, the concentration of neurotransmitters within the synapse or within the presynaptic neuron is altered. These changes lead to signal transduction and secondary cell signalling within the postsynaptic neuron, eventually impacting transcription processes within the nucleus that lead to the development of new enzymes and proteins. Ultimately, antidepressants are thought to remodel neural networks by facilitating neurogenesis. The table shows the specific receptor interactions of various antidepressant molecules and their effects on monoamine transporter systems. These actions are used to group antidepressants into classes, although considerable overlap in the actions of different medications occurs and downstream processes probably converge. 5-HT=serotonin. R=receptor. T=transporter. NA=noradrenaline. HI=histamine. DA=dopamine. MAO=monoamine oxidase. mBDNF=mature brain-derived neurotrophic factor. TCAs=tricyclic antidepressants. NDRIs=noradrenaline dopamine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors. SNRIs=serotonin-noradrenaline reuptake inhibitors. Adapted from Willner et al,[54] by permission of Elsevier.

comparisons, and many of the same drugs did better than other antidepressants (eg, amitriptyline, mirtazapine, venlafaxine, paroxetine, and vortioxetine); however, analyses on aggregated data cannot identify effects at the individual level, and therefore, in practice, antidepressant prescription remains a matter of clinical judgment. Nevertheless, the finding that antidepressants are an effective treatment for major depressive disorder, despite high placebo responses, is reassuring. Furthermore, some medications are probably well suited, both in terms of efficacy and tolerability, to some types of depression, and can be tailored accordingly. Two examples are administering sedative antidepressants for depression with anxiety or insomnia, and activating antidepressants for depression with psychomotor retardation. Although reliance solely on the use of depressive symptomatology to select which antidepressant will work best is also not yet feasible (figure 3), combining this knowledge with clinical acumen does inform and improve management.

Managing suboptimal response
Despite the variety of therapies available, a substantial proportion of patients do not respond adequately to the various treatments prescribed, having either a partial

response or no response at all.[34,122] Within the framework of a randomised trial, the sequenced treatment alternatives to relieve depression (also known as STAR*D)[123,124] study examined many standardised steps in the management of major depressive disorder, using medications and cognitive therapy within both primary care and psychiatric settings. The study sought to examine the more clinically meaningful goal of remission, as opposed to response, and found that cumulative remission after four treatment steps was still only two-thirds (67%). The remission at each of the steps was 36·8%, 30·6%, 13·7%, and 13%. Although disappointing in comparison with results from clinical trials, the findings reflected real-world clinical experience, since patients often require a series of treatments and the use of several strategies to achieve remission. Such suboptimal response is often subsumed under the broad descriptor so-called treatment-resistant depression—a problematic term that has proven difficult to define, because of the heterogeneity of depression and the lack of a standard, algorithmic approach to treatment.[125] The term is also misleading because it suggests that the illness itself is somehow resistant to treatment, when in fact many factors contribute to non-response, and these relate largely to how treatment is provided, and in what context.[126] For example, alongside depression, psychiatric and medical comorbidities often complicate illness management and reduce the likelihood of responsiveness. Similarly, patient-related factors, such as willingness to pursue treatment as prescribed, personality, and age contribute to whether a course of treatment is likely to be successful. Generally, two-thirds of patients with depression will not remit with initial antidepressant treatment and, therefore, require careful reappraisal.[4,35] In addition to exploring the factors already outlined, the diagnosis of depression should be carefully reviewed to exclude an alternative explanation, such as bipolar disorder or a personality disorder.

The treatments that can be used to tackle non-response are much the same as the options available when initiating treatment, but additional methods can be used with the aim of increasing efficacy.[127] In general, the addition of psychological therapy to pharmacotherapy or vice versa has been found to be helpful.[128] Psychotherapeutic engagement enhances medication compliance, and difficulties with pharmacotherapy are likely to become evident earlier. To increase the efficacy of antidepressant medication, especially in instances where it might not be reaching its target, one simple strategy is to increase the dose of the antidepressant.[129] However, this result is not an increase of efficacy per se, and no clinically significant benefit has been found when dose escalation has been tested following initial non-response to standard-dose pharmacotherapy.[130] Nevertheless, an increase in dose could overcome pharmacokinetic limitations. For example, some drugs are metabolised quickly and can require higher oral doses to achieve necessary plasma concentrations. Furthermore, in some instances, dose escalation can increase the bioavailability of medication and enhance its receptor binding.[131] This strategy is particularly useful for drugs that have a broad therapeutic range (eg, amitriptyline and venlafaxine).[132,133]

Augmentation is another strategy to overcome non-response. This strategy involves adding a drug that enhances the antidepressant effects of the medication already being prescribed. The most common strategy, and one that is effective in augmenting the actions of almost all antidepressants, is adding lithium.[134] Once a steady plasma concentration has been achieved, the effect of lithium augmentation is usually evident between 1 week to 10 days. The effective dose of lithium for augmentation is equivalent to that used for maintenance therapy of bipolar disorder (plasma concentrations of 0·6–0·8 mmol/L), although lower doses and plasma concentrations can also be effective.[135] Once lithium augmentation has produced a therapeutic response, the combination should be maintained as the withdrawal of either drug (antidepressant or lithium) is likely to result in relapse.[134]

Even though lithium augmentation is the most widely researched strategy, augmentation with atypical antipsychotics has become popular.[136,137] This increase in popularity is because the atypical antipsychotics commonly used as augmentation strategies (quetiapine and olanzapine) are both sedating and anxiolytic, even in small doses.[138] Therefore, when prescribed alongside antidepressants, these atypical antipsychotics immediately aid sleep and anxiety, and counter some of the acute side-effects of antidepressants until the antidepressant becomes effective. It is important to emphasise that the use of atypical antipsychotics is not widely indicated, and much of the evidence for this strategy is empirical.[139] However, emerging evidence from clinical trials supports the use of atypical antipsychotics for augmentation while remaining aware of potential treatment-related side-effects.[137] Furthermore, whether this strategy truly augments the actions of antidepressants is unknown and, because of the side-effects associated with these drugs when prescribed long-term, the addition of an atypical antipsychotic to an antidepressant should only be considered a short-term strategy. In some instances of poor response, triiodothyronine (T3) has been used to augment the effects of antidepressants to good effect,[140,141] and stimulants have also been used.[142]

When patients do not respond to increased dose, augmentation, or a combination of both strategies, combinations of antidepressants can be prescribed if a pharmacological synergy between medications exists because of their therapeutic profiles (eg, combining venlafaxine with mirtazapine).[143,144] Nevertheless, the benefits of such strategies are largely untested. Another

alternative is to switch to a new antidepressant, usually with a different mechanism of action.[145] However, switching to a different antidepressant risks losing any benefit the current medication regimen has attained, and usually this strategy takes longer to implement than increasing the dose of an antidepressant already in place, or augmenting its actions. Alongside psychological and pharmacological strategies, when tackling poor response, electroconvulsive therapy is a useful alternative, especially if the depression has melancholic or psychotic features. Psychotic depression should be treated from the outset with both an antidepressant and an antipsychotic medication, unless the decision is to immediately use electroconvulsive therapies.[146]

Finally, all these strategies require careful and frequent monitoring from the outset to help compliance and maximise response. Non-response is sometimes an indication that the diagnosis is incorrect, and re-evaluation of both diagnosis and the strategies used is necessary before trying more sophisticated treatments.

Special populations
The manifestations and management of depression are affected by life stage and special circumstances, such as during the perinatal period. For children and adolescents, the clinical presentation of depression and response to treatment can differ from adulthood, because of developmental differences in biology and psychophysiology in children and adolescents, and limited language and experience, which means they are likely to express their distress differently.[147,148] Comorbid medical problems, cognitive compromise, and a greater causal role for vascular disease are more pronounced with increasing age, altering the clinical presentation and impacting management.[149,150] We discuss the considerations about these age groups, along with major depression occurring in the perinatal period,[151,152] in the appendix. In practice, these episodes of depression more commonly require treatment by a psychiatrist.

Future directions
The fact that major depression affects many people, and has a huge impact on the individuals and imposes an immense economic burden, means that greater efforts are required to improve its diagnosis and management. This need applies especially to low-income and middle-income countries, where health-care resources are limited at every level. The heterogeneity of the illness, the stigma surrounding mental illness, and a collective failure to identify more effective treatments are key challenges. However, the primary problem is that our knowledge of the aetiopathogenesis and pathophysiology of major depressive disorder is incomplete and has (so far) not provided a sufficient understanding to develop more effective treatments. Prevention, early intervention, and effective management are all crucial goals, but meaningful advances are only probable if basic causal mechanisms can be identified. In clinical practice, the goal of treatment must shift from response to remission, and, in the future, we should seek to achieve recovery and the development of resilience. Regarding these objectives, we seek earlier detection and diagnosis, and prompt treatment of depression when it first emerges. Major depression is fundamentally an illness of the brain, and this disorder is likely to be preventable, and even curable, once its aetiopathogenesis is fully known. To make that happen, substantive and long-term investment is required for research that makes full use of recent advances in neuroscience, genomics, and technology.

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