Depression

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Depression is a common illness that affects people within every society around the world. It afflicts the young and the old and everyone in between, and as such poses an immense global burden. New interventions and a deeper understanding of this illness are emerging, but improving the use of existing treatments is equally important and might be a more efficient and effective strategy to addressing depression. Therefore, it is imperative that we improve the diagnosis of depression and its clinical management.

Introduction

Depression affects approximately a quarter of a billion people globally, of all ages and from all walks of life.[1,2] In this Seminar, we focus on depression in adults, which causes functional impairment, affects relationships and work, and is costly to the individual and society as a whole.[3,4] The psychosocial impact of this profoundly stigmatising illness is deep and simultaneously far-reaching.[5,6]

Epidemiology

Prevalence

The global prevalence of depression varies,[7] with socioeconomic and cultural factors, as well as stigma, playing a substantial role.[8] Absolute case numbers and rates of depression continue to increase,[7] and depression globally is greater in women than in men (2:1), with the gender gap remaining relatively consistent throughout adulthood following puberty[9,10]—a difference attributed in part to differential hormonal and developmental changes.[9,11]

Depression typically begins in the second decade of life, with nearly 40% of people with depression having their first episode before age 25 years.[2,12] By its nature, it is recurrent and nearly a quarter of people will have a further episode within 5 years of onset,[13] and the likelihood of additional episodes increases once recurrence is established. In general, one in 15 adults have depression in any year and a fifth of people experience depression in their life;[1,2,14] however, the true rates of depression are probably higher.

Course and prognosis

In community settings, most depressive episodes remit after 2–6 months and resolve within a year,[15,16] but in primary and secondary care settings, between a third and a half of patients remain unwell for more than a year, and most patients have further episodes,[17] with a recurrent pattern more likely in patients with early onset.[10]

Causes and mechanisms

Research examining the precursors, onset, and response to treatment of depression has identified probable causal factors and mechanisms.

Contemporary concepts of depression draw on diverse molecular,[18] genetic, psychological, and social mechanisms, but none of these concepts fully explain the illness satisfactorily.[19] New neuroscientific and psychological models implicate neural networks,[20,21] cardiovascular systems,[22] neuroendocrine systems,[23] and the gut microbiome.[24] In addition, inflammation caused by stress creates so-called scars of depression in both bodily and brain systems.

In this Seminar, we focus on our current understanding of depression (figure 1)[26–30] based on the diathesis-stress model,[31] which is used to inform clinical diagnosis and management and helps provide patients with meaningful causal explanations. The diathesis-stress model suggests that depression might be caused by a combination of a stressful event and individual vulnerability. Furthermore, this model serves as a useful schema for the multitude of depression-related factors that emerge from biological, psychological, and social determinants (panel 1).[8]

Search strategy and selection criteria

In this Seminar, to capture the many facets of depression, we drew on our unique expertise (psychiatry [GSM], primary health care [AS], nursing [C-YW], lived experience [AN], and psychology and neuroscience [VK and EB]) and clinical experience, and evidence from primary sources in relation to depression in adults was appraised collectively. Throughout this process, the Seminar was co-produced with an author with lived experience being involved from the outset. We drew upon recently published international guidelines and their analysis of evidence for the efficacy of various treatments, including those for the UK, Canada, the USA, and Australia and New Zealand, the Mental Health Gap Action Programme (mhGAP) Guideline for Mental and Neurological and Substance Use Disorders, and the World Federation of Societies of Biological Psychiatry. Some guidelines such as the mhGAP require minimal training, which is ideal for primary care. Additionally, PubMed, APA PsycInfo, and Cochrane were searched using the search term "depressi*" or "mood disorder*" combined with other terms related to screening, diagnosis, formulation, and management. We restricted the search to papers from Jan 1, 2021, to Sept 1, 2025, with a focus largely on meta-analyses and systematic reviews and original research articles where relevant. The reference lists of included articles were scanned for relevant information and seminal articles outside this range have been included, where deemed helpful or necessary. A full list of search terms can be found in the appendix (p 18). Separately, based on the data and in conjunction with clinical experience, we developed clinical advice for physicians and health workers in primary care and psychiatric services, specifically for general practitioners, psychiatrists, and psychologists. We have indicated areas in which evidence is absent or as yet insufficient. Clinical suggestions and recommendations have been made with treatment interventions in mind to inform therapeutic decision making and facilitate pathways of care (eg, treatment choices). Where possible, essential knowledge has been summarised and presented in figures to facilitate learning and understanding.

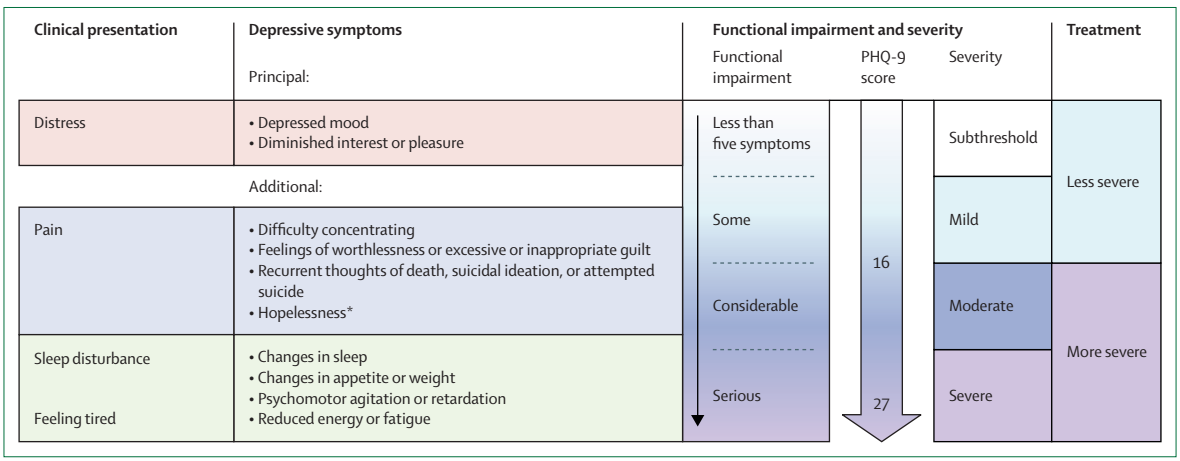

Figure 1: **Diagnosing depression**
The diagnosis of depression involves three components: (1) eliciting the symptoms that form a depressive episode; (2) determining their severity and the functional impairment that they cause; and (3) mapping their longitudinal course over the duration of an episode, as well as the illness as a whole. Depressive episodes usually last several weeks and can last several months if untreated. After remission, symptoms can re-emerge (relapse) before functional recovery and even then, further long-term episodes of depression (recurrence) remain likely. Scores and categories drawn from UK National Institute for Health and Care Excellence.[25] PHQ-9=Patient Health Questionnaire-9. *Hopelessness is only specified in ICD-11 and not in DSM-5-TR.

Diagnosis

Screening and detection

Distress caused by depression prompts individuals to seek help, and informal assistance from friends and family, and searching the internet for solutions, which are usually sought before consulting a professional.[32–34] In part, such delays also occur due to the stigma associated with mental illness and difficulties accessing care. Consequently, weeks or months might pass before individuals receive professional help, and often individuals are not properly diagnosed for years after initially seeking help.[35,36]

Greater depression awareness and access to screening have increased presentations and treatment uptake.[37,38] However, the use of screening tools alone can both fail to detect serious illness and overdiagnose depression, leading to mistreatment.[33,39] Therefore, screening alongside clinical evaluation is optimal, and hence screening measures are increasingly being used in primary care to inform medical consultations;[33,39] in practice, simply asking about two symptoms over the past 2 weeks, as per the Patient Health Questionnaire-2, can be sufficient for detecting depression (appendix pp 3–4).

Diagnosing depression

The major taxonomies (ICD[40] and Diagnostic and Statistical Manual of Mental Disorders [DSM][41]) provide standardised diagnoses for depressive disorder (ICD-11) and major depressive disorder (DSM-5-TR; figure 1; for descriptions of additional depressive disorders, see the appendix [p2]). These descriptors refer to the entirety of the illness over the course of a person's lifetime and should not be confused with depressive episodes, which are acute exacerbations. The principal features of depression are low mood and anhedonia (an inability to gain pleasure from activities the person usually finds enjoyable); in total, the person must have a minimum of five symptoms occurring most of the time and for at least a fortnight, with the number of symptoms broadly reflecting illness severity and causing functional impairment (figure 1). However, before making a definitive diagnosis of depression, it can be useful to assign a provisional diagnosis.

In practice, the diagnosis of depression usually starts as a clinical suspicion that is confirmed or refuted by further questioning. A family history of depression or recent life events provide additional clues that can help make a provisional diagnosis, but due to limited consultation time or because the illness is still evolving, these factors might be all that is possible during the initial stages of presentation. If depression is suspected, another appointment should be scheduled and the patient should be asked to monitor their mood, sleep, and activities in the interim. If possible, partners, family, and carers should be recruited as they can corroborate information and their engagement helps validate the patient's distress.

Clinically, diagnosing depression involves eliciting key symptoms and determining their impact on an individual's life, as well as charting their pattern over time to map the course of the illness. In practice, patients seldom present spontaneously with low mood or sadness, and instead usually complain about general distress, sleep disturbances, pain, and fatigue. Therefore, it is useful to have in mind depression as a potential diagnosis and routinely ask about its key symptoms (figure 1), and if depressive symptoms are identified, to gauge their severity and the functional impairment that they cause, as this informs diagnosis and management (figure 1).

Together, the number of symptoms, their severity, and the functional impairment that they cause provides a

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See **Online** for appendix

Panel 1: **Depression vulnerability factors**

Biological and physical health factors

Immutable factors

- Family history of mental illness*
  - Mood disorder
  - Substance misuse
- Epilepsy
- Intellectual disability
- Head injury
  - Concussion
  - Traumatic brain injury

Modifiable factors

- Physical condition
  - Cardiovascular (eg, hypertension and cardiovascular disease)
  - Neurological (eg, dementia and Parkinson's disease)
  - Metabolic (eg, diabetes and hypothyroidism)
- Lifestyle
  - Unbalanced diet
  - Lack of or irregular exercise
  - Deprivation or non-restorative sleep
  - Poor sleep hygiene
  - Smoking and consumption of drugs and alcohol

Psychological and mental health factors

Immutable factors

- Personal history of mental illness
  - Mood disorders (eg, depression and bipolar disorder)
  - Substance misuse (eg, alcohol and cannabis)

Modifiable factors

- Mental condition
  - Anxiety
  - Psychosis
  - Eating disorders
  - Substance use
- Personality
  - Insecure attachment
  - Negative self-concept
  - Sensitivity to rejection
  - Negative emotionality
  - Perfectionism
  - Pessimism
  - Low resilience
- Maladaptive coping strategies
  - Rumination

Social and economic factors

Immutable factors

- Previous stressful life events
  - Loss (eg, death of parents, siblings, or spouse; financial loss; or loss of identity)
- Past experience of abuse
  - Childhood abuse (physical, emotional, or sexual)
  - Partner or parental abuse (verbal, physical, sexual, or financial)
  - Bullying at school by peers or teachers
  - Harassment and bullying by co-workers and managers

Modifiable factors

- Current experience of abuse
  - Parental or partner abuse (verbal, physical, sexual, or financial)
  - Workplace harassment and bullying by co-workers, line managers, or organisation
- Lack of social support
  - Social exclusion due to one's values, belief, or identity
- Low socioeconomic status
  - Unemployment
  - Low income
  - Unstable housing
- Threats to safety and security
  - Unsafe living conditions
  - Insecure housing
  - Persecution and war

*Family history of mental illness reflects not only biological vulnerabilities via genetics, but also environmental risk factors associated with mental illness (eg, effects on parenting) as well as contextual risk factors (eg, poverty).

measure of the overall severity of a depressive episode, which can be broadly categorised as less severe or more severe. Describing depression in this manner allows treatment to be informed by recommendations made by various guidelines,[42–44] particularly those made by the UK National Institute for Health and Care Excellence (figure 1).

Sometimes a diagnosis cannot be made immediately in clinical practice, and appraising the patient over a short period of time is useful—a process called watchful waiting (panel 2). During this time, mood monitoring (panel 3) can be commenced, and this might also help with diagnosis and assist with subsequent tracking of any treatment response. Digital health technologies are especially useful in this regard as they signal to the patient that a proactive approach has been adopted. Receiving a diagnosis of depression and starting treatment are inherently stressful, and commencing antidepressant treatment can occasionally increase the risk of self-harm (panel 4). Therefore, the diagnosis and management of depression should be fully explained to the patient from the outset, and the probable prognosis and potential adverse effects of treatment should be discussed.

Managing depression

Planning and implementing treatment

Treatment can be planned once the symptom profile and severity of depression have been characterised. First, the patient's experience and treatment preferences should be

considered within the context of practical limitations such as treatment availability, access, and cost.[4,55] When possible, treatment choice should be evidence-based and draw upon expertise, and treatment options should be aligned with clinical features of the illness while considering patient characteristics such as age, gender, and individual circumstances.[56]

The initial goal of treatment is to relieve distress and achieve remission. Once depressive symptoms subside, the subsequent aim is recovery, after which the emphasis shifts to preventing recurrence.[57] Successful treatment of depression often requires a combination of interventions, which can be administered concurrently and sequentially; a multifaceted strategy should be used whenever possible and individual interventions should be selected with a view to maintaining them. The settings in which treatment will be administered, and by whom, should be considered, and if a specialist (eg, a psychiatrist or psychologist) will be needed, then prompt referral and engagement should be considered from the outset of management.

Once management is under way, the individual's clinical symptoms should be continually reassessed and treatment tailored accordingly. In practice, this involves confirming the diagnosis and assessing treatment response at every clinical encounter, especially when making changes to treatment. Concurrent life stressors can exacerbate depression, and it is important to know about an individual's supports and any obligations they might have (eg, working or caregiving responsibilities).[25,42,44] Careful monitoring is important because comorbid psychiatric illnesses such as substance use or anxiety disorders are common and can complicate treatment, and also because depressive episodes might represent an emerging bipolar disorder, which only becomes evident once mania manifests.[58,59]

Most cases of depression can be treated successfully using four broadly complementary therapeutic strategies: psychoeducation, lifestyle modifications, psychological interventions, and pharmacotherapy.[25,42,44] A fifth strategy is physical treatments (eg, electroconvulsive therapy and other neuromodulators), which are mostly used to treat severe depression that has not responded to other treatments or requires hospital admission for specialist management. However, since physical treatments are used less often than the other strategies, they are not discussed in this Seminar. In contrast, psychoeducation is integral to the management of depression and should be instituted from the outset.

Psychoeducation

Generally, psychoeducation involves providing knowledge and instruction about an illness and its management in an unstructured or formal manner to the patient and their carers.[60,61] Evidence for psychoeducation in the prevention and treatment of clinical depression is scarce, but it has been shown to benefit those with chronic diseases.[62,63] It

Panel 2: Watchful waiting in primary care

Diagnosing depression requires a person-centred approach. General practitioners (GPs) are suitable for this approach as they provide whole person care in the context of a doctor–patient relationship.[45] Formulating depression requires skilful integration of biopsychosocial and biographical information and GPs are well positioned in this regard as the patient is usually well known to them. This familiarity also enables GPs to distinguish between situational crises and clinical depression and function as gatekeepers as they determine which pathway of care to pursue and when to refer to a specialist.[46] This process is sometimes called watchful waiting[47] as it takes time and entails careful appraisal. During this time, which can vary considerably from days to weeks, collateral information can be sought, and investigations that help exclude medical causes of depression, such as anaemia and hypothyroidism, can be conducted; this approach is also helpful because it lends further credence to the patient's distress. Hence, watchful waiting is in fact an active process that allows other sources of distress such as pain or infection to be treated, and its principal aim is to allow sufficient time to lapse so that a proper diagnosis of depression can be made and suitable management can be determined. However, watchful waiting is not always appropriate, for example, in crisis situations such as severe depression or suicidal risk, in which practical steps might need to be taken immediately to treat the patient and ensure their safety. In these cases, mood monitoring should be instituted.[47]

Panel 3: Mood monitoring

Once depression is being considered by a health-care professional, patients should record their clinical symptoms, sleep, and physical activity. Asking patients to monitor themselves helps them and the health-care professional to understand the nature of their symptoms and provides a longitudinal record that is less reliant solely on the patient's long-term recall.[48,49] Monitoring symptoms is also useful during management as it helps evaluate treatment outcomes.

Digital health technologies—any form of technology for health care, such as the use of smartphones to monitor health or provide guidance—could assist with mood monitoring.[50] The term also refers to messaging, digital phenotyping, and the use of wearables such as activity trackers, as well as the use of telehealth and videoconferencing.[51] Digital health technologies are used to provide psychoeducation, reminders, mood monitoring, and the delivery of psychological interventions.[52]

Panel 4: Suicidal thoughts and risk of suicide

Suicidal thoughts often occur in the context of depression and can be confusing as they are a diagnostic feature of the illness (figure 1) but also a cause for concern. Thoughts about suicide are usually driven by critical thoughts about oneself, one's relationships, and one's situation in life. Negative thinking and feelings such as guilt can fuel a sense of helplessness and lead to a loss of hope, which can prompt thoughts about ending one's life, especially to avoid continuing psychological pain.[53] Therefore, when assessing a patient with depression, it is important to enquire about thoughts of suicide or self-harm, and when formulating an individual's risk of self-harm or suicide, examining their specific needs and how best to ensure their safety is crucial. Regarding suicidal thoughts, it is important to assess their nature (frequency, duration, and content), as well as the process of suicidal ideation (the individual's conviction and intent and any plans they might have made). Ideally, a formulation of suicide risk should include consideration of historical factors (eg, previous suicide attempts), recent difficulties, and the availability of resources such as family support.[54] If there is serious concern regarding a person's safety or there is an ongoing risk of self-harm, a referral should be made to specialist or emergency services, and hospitalisation might be indicated.

Panel 5: Risky lifestyle habits

In most countries, it is legal to smoke tobacco and drink alcohol and therefore they are by far the most common risky lifestyle habits, and their use is well documented and researched.[64]

Alcohol misuse

Links between alcohol misuse and depression are both direct and indirect as alcohol is a depressant, and once dependent, individuals continue to misuse alcohol to transiently alleviate stress.[65-67] Managing depression in the context of alcohol misuse (dual diagnosis) is complicated and usually requires specialist services. Many specialist services treat the two disorders concurrently. However, in most cases, substance misuse must be tackled first before depression can be treated.[68] This is because addressing alcohol consumption often reduces depressive symptoms,[69] and implementing strategies to address problematic alcohol use early in the management of depression (eg, with psychological interventions) increases the chance of benefiting from depression treatments.[70]

Smoking tobacco

Smoking is linked to heart disease, cancer, and metabolic disorders; there are no health benefits from this habit even though the inhalation of nicotine is initially anxiolytic. This anti-anxiety effect soon diminishes with repeated use and gives way to nicotine craving. Such gradual habituation and dependence are also evident in those who vape, and this is particularly concerning as this habit is increasingly common in adolescents and young adults.[71] Contrary to the misconception that smoking cessation might increase anxiety and depression,[68] those who stop smoking usually experience an improvement in ensuing months for these symptoms.[72]

also informs patients' expectations and helps them accept that they have a chronic condition. In addition, psychoeducation enhances doctor–patient engagement and therapeutic adherence,[60,62] while also instructing patients on how to monitor their illness. Therefore, whenever a suitable opportunity arises, clinicians should educate patients about the likely causes and clinical symptoms of depression, and its treatment and prognosis.[60]

Lifestyle modifications

In depression, healthy lifestyle factors (eg, diet, exercise, and sleep) and risky lifestyle habits (eg, smoking tobacco, drinking alcohol, and using substances) have been shown to play an influential role. Therefore, alongside modifiable healthy lifestyle factors, risky lifestyle habits commonly associated with depression (in particular smoking and drinking, which are amenable to change albeit with greater difficulty) should also be addressed (panel 5).[73,74]

Healthy lifestyle factors

Balanced diet, regular exercise, and proper sleep prevent or at least delay the onset of depression.[75] Furthermore, diet, exercise, and sleep are inherently entwined such that change in one affects the other two, hence their grouping as healthy lifestyle factors. Each factor has a biological and psychological component, and in practice, the most common problem is their disruption, which can lead to depression or exacerbation of existing symptoms.

Exercise

International guidelines recommend exercise to treat the symptoms of less severe depression and improve sleep quality and cognitive function.[25,42,44,76] This recommendation is supported by meta-analyses of controlled treatment studies in adults with depression that show that exercise produces tangible benefits with an overall moderately large effect size.[77,78] Research examining the benefits of various types of exercise in adults with depression highlights some specificity according to age and gender (figure 2A). For instance, aerobic exercise, walking, and jogging, as well as strength exercises and yoga, are on par in terms of efficacy with cognitive behavioural therapy (CBT),[78] and evidence for each of these activities is strong, positioning them as more effective than selective serotonin reuptake inhibitors (SSRIs). Furthermore, although there is no clear age or gender specificity for general exercise (eg, walking, jogging, and aerobic exercise), strength exercises produce greater improvements in younger adults and women. Conversely, yoga is of greater benefit to men and older individuals. The reasons for certain exercises being efficacious are multifaceted and might include other factors such as social interaction and skill acquisition (figure 2). Additionally, exercise is more beneficial when structured (time of day and frequency) and undertaken in combination with psychological interventions and medications (eg, SSRIs) and its benefits extend into old age.[77] Thus, in addition to its general health benefits, exercise is particularly useful in the treatment of depression as it alleviates symptoms and can prevent onset and recurrence.[84,85]

Diet

Growing interest in whether modifying diet can treat and perhaps prevent depression has led to increasing calls for clinicians to be aware of the potential benefits of different types of diet and to play a role in implementing dietary change.[86] The links between diet and depression are less direct than those found in other illnesses such as diabetes,[87] but gut microorganisms, stress hormones, and brain neurotrophins have all been shown to actively affect the immune, inflammatory, and hypothalamic–pituitary axes in depression.[88–90] Nevertheless, specific dietary excesses and deficiencies that predictably lead to depression are yet to be determined, and the main benefit of certain diets seems to be the prevention of depression, possibly by reducing inflammation.[86,91]

Recent research studies examining the relationship between diet, mood, and the gut microbiome[92] have yielded new insights. However, more research is needed before specific recommendations can be made to predictably alter mood through changes to the gut microbiome, especially as most findings are based on animal studies[83,92] and human dietary patterns vary considerably.[93] Furthermore, the properties of ingested food are relatively distal to putative mood effects within

the brain. Nonetheless, a Mediterranean diet significantly benefits mood[94,95] and diminishes the risk of depression, possibly because it contains healthy food groups and has a low inflammatory index.[96,97]

Studies examining specific foods from a broad range of food groups have also found similar but modest benefits that require replication.[98] Conversely, ingesting excessive ultra-processed foods and refined sugars and having a proinflammatory diet increases the likelihood of depression.[99] Therefore, a balanced, healthy diet containing Mediterranean diet food groups could benefit mood in people with depression.[94,95]

Sleep

In depression, patients often have disturbed sleep (sleep dysfunction), which they describe as difficulty sleeping (insomnia) and waking too early (early morning waking), which typically manifest as too little sleep (reduced duration) and poor-quality sleep (lack of slow-wave sleep). Sleep problems such as these can be addressed using medications but are initially best managed using non-pharmacological interventions.[100,101]

Establishing good sleep hygiene by modifying lifestyle habits and improving exercise and diet is important initially.[102] CBT, which addresses anxiety and negative cognitions, is the most effective strategy for improving sleep,[100,101,103] although exercise is also beneficial, especially in combination with other interventions.[101,104] Bright-light therapy, which acts via the suprachiasmatic nucleus,[105,106] might also be beneficial, especially for subjective sleep quality,[107] but the effect is stronger in combination with antidepressants and particularly in seasonal depression.[105,108]

Other psychological strategies (eg, meditation techniques such as mindfulness and body scanning) and physical interventions (eg, hypothermic bathing and acupuncture) appear to do no harm, but they do not seem to be particularly beneficial either.[104] Therefore, despite multiple options for modifying sleep without needing medication, there is only strong evidence for CBT and exercise to date,[99,100] and in individuals with either seasonal depression or depression with substantial phase-shifting of sleep, bright-light therapy might provide some modest benefit.[105,106]

If non-pharmacological approaches for sleep dysfunction are ineffective then pharmacological treatments for sleep can be considered (panel 6; figure 2C).

Psychological interventions

Most patients favour psychological interventions to address their depression; psychotherapeutic approaches inherently create a therapeutic relationship that increases treatment satisfaction and adherence.[117] This therapeutic bond plays an important role when combining psychological interventions with other treatments, and in practice, although psychological interventions have an independent effect, combination therapy is more effective than individual therapies.[25,118,119]

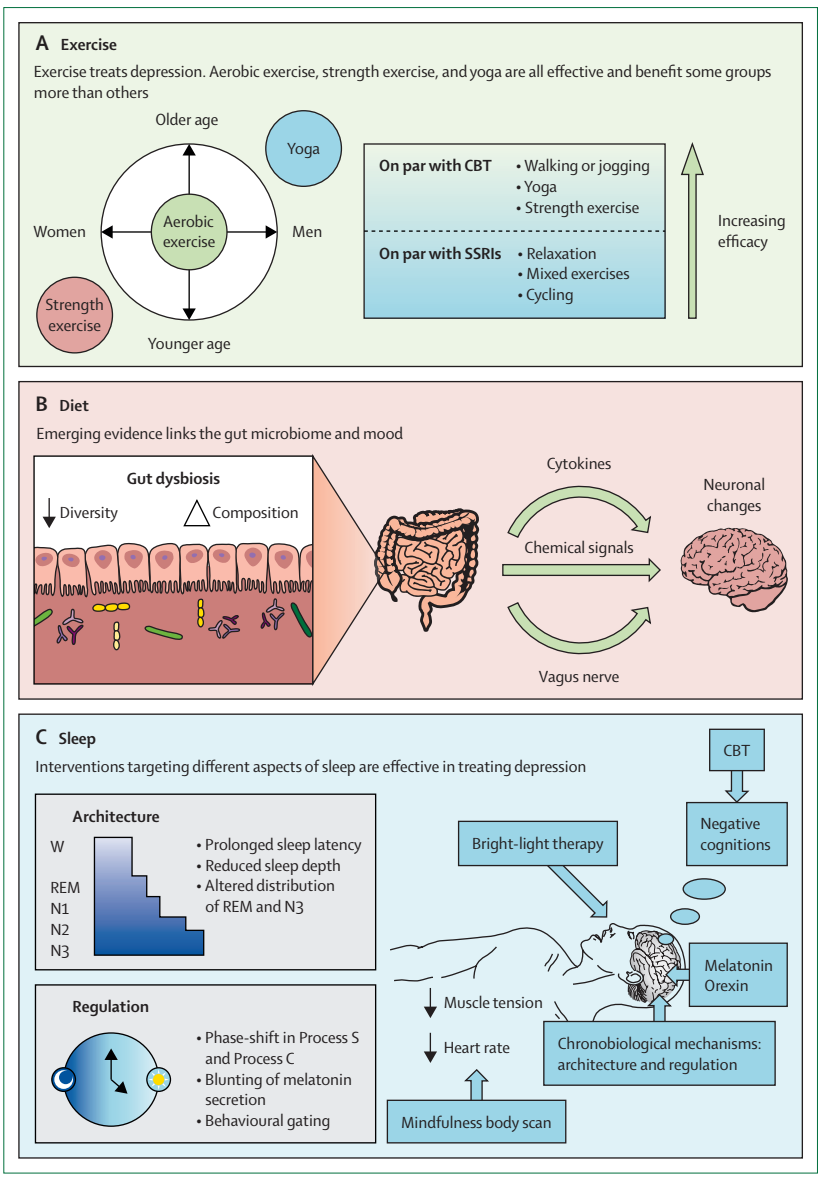

Figure 2: **Lifestyle modifications**
(A) Exercise is an effective treatment in depression and shows some specificity with respect to age and gender.[78] (B) The gut–brain axis is thought to be bidirectional and operate through a number of pathways in depression,[79] such as neural pathways (vagus nerve),[80] via inflammatory and immune signals, and through chemical signals,[81] all of which are inter-related.[82] Changes in the composition of gut bacteria (gut dysbiosis), as well as a lower overall diversity of gut flora, have been associated with depression.[83] (C) Sleep dysfunction is strongly implicated in depression, and both the architecture of sleep and its regulation are impacted. Sleep architecture typically involves four stages: after waking (W), rapid-eye-movement sleep (REM), light sleep (N1), deeper sleep (N2), and slow-wave sleep (N3). In individuals with depression, the regulation of sleep can be affected through a phase-shift in both homoeostatic sleep (Process S) and circadian sleep (Process C), as well as an insufficient Process S. This results in insomnia and sleep that is non-restorative, which can affect mood and functioning. The various interventions for sleep act via different mechanisms. CBT=cognitive behavioural therapy. SSRIs=selective serotonin reuptake inhibitors.

General principles

When choosing a psychological approach, the psychological symptoms, severity of depression, and individual characteristics of a patient that might influence their treatment response should be considered.[120,121] Common psychological targets include negative cognitions and

Panel 6: Sleep pharmacotherapy

Benzodiazepines and related medications can be effective sedatives if used in the short term (<4 weeks), but their use to modify sleep to treat depression is less well mapped and their prescription (both as monotherapy and adjunctive treatment to antidepressants) does not show sustained benefits. These medications should therefore be prescribed with caution and only for a limited time, after which they should be discontinued with gradual dose reduction.[109] Tricyclics have long been used to aid sleep and treat depression,[110] and more recently, antipsychotics that are sedating (eg, quetiapine) have been prescribed for similar reasons[110,111] as they help with initial insomnia and short-term relief of anxiety.[112] However, the adverse effects of these medications limit their benefit in the long term. Other medications that are used for sleep (eg, melatonin and orexin) appear to be effective in instituting normal sleep cycles, but again, specific benefits in the context of depression have not yet been established.[113–116] Notably, melatonin supplementation has only shown significant efficacy at higher doses and after 12 weeks of treatment,[114] and orexin antagonists have not shown consistent effectiveness in the treatment of depression.[113]

interpersonal issues (appendix pp 8–11). Regarding severity, grading depression as less or more severe can be useful (figure 1),[25] but more granular gradation[55] does not further inform treatment choice.

Efficacy of psychological interventions

CBT, interpersonal therapy, behavioural activation therapy, problem-solving therapy, and mindfulness-based therapies, as well as short-term psychodynamic psychotherapy, all benefit patients with depression.[25,122] Of these, CBT is the best researched and most widely available,[123] and although particular therapies conceivably engage specific psychological targets, there is insufficient evidence to show significant differences in efficacy between the various approaches.[25,122,124,125] One reason why differentiation of psychological therapies in terms of efficacy is difficult is that they all share some elements.[126] Their effects on depressive symptoms are also thought to be mediated by shared cognitive mechanisms (eg, change in dysfunctional attitudes for both CBT and interpersonal therapy). However, some therapy-specific mechanisms could also play a role (eg, change in experiential avoidance for acceptance and commitment therapy but not for CBT or interpersonal therapy).[127,128] Hence, the neural mechanisms implicated in the psychological effects of these interventions appear to overlap (eg, top-down modulation reducing dysfunctional thought processes),[129] while some networks seem therapy-specific. Therefore, tailoring psychological interventions in practice is useful, as well as targeting specific symptoms so that therapy is structured and meaningful.

In addition to the benefits of acute treatment, considerable evidence points to the efficacy of psychological interventions in relapse prevention,[130,131] with ongoing psychological engagement helping prevent future depressive episodes and enabling prompt intervention.[132] Furthermore, psychological interventions have also been shown to be effective for individuals who have partially remitted, with therapy reducing residual symptomatology and the risk of relapse across a broad range of patient characteristics and treatments.[133]

Regardless of illness severity (figure 1), psychological therapies delivered in one-to-one or group settings, and when administered in combination with medications, are better than treatment as usual.[25] In community care, treatment as usual might involve psychoeducation or antidepressant medication, or both. However, based on the effect sizes observed across studies, CBT and behavioural activation therapy appear to produce greater symptom reduction when delivered in a group setting than one-to-one sessions in less severe depression, whereas one-to-one sessions are more effective than group therapy in more severe depression.[25] Nevertheless, in-person individual therapy is regarded as the gold standard of psychological interventions in practice, even though there is insufficient access to individual CBT in many settings around the world due to scarce availability and high cost. Consequently, alternative settings and means of delivery such as group and internet-based therapy are popular, and in many cases these more cost-effective and accessible options appear to be equally effective.[25,44,134,135] Indeed, the greater effectiveness of CBT is clearly evident when compared with long-term pharmacotherapy.[136]

Digital health technologies for psychological interventions

The uptake of digital health technologies has increased in recent times because they can be accessed independently without necessarily relying on support from others (ie, they can be unguided, self-directed, or guided or facilitated).[137]

In guided programmes, the facilitator might have clinical expertise and help drive engagement, which can either be delivered live (synchronous; occurring at the time the individual is engaging with digital health technologies) or delivered later (asynchronous). Generally, guided digital health technologies have been found to be more effective than those that are self-directed,[137,138] and internet CBT (i-CBT) produces significant effect sizes when guided,[139] with benefits persisting beyond 12 months.[140]

When considering severity in less severe depression, i-CBT shows greater benefits than treatment as usual or waiting list,[25,141] with emerging evidence that text-delivered CBT is also an effective option.[142] In more severe depression, guided i-CBT seems to produce larger symptom reduction compared with non-guided i-CBT.[25,141] Notably, there is no significant difference between guided and unguided i-CBT for less severe depression.[141] Therefore, i-CBT is

recommended as a first-line monotherapy for less severe depression and adjunctive use is recommended for more severe depression,[42,141] with guided therapy being preferable for more severe depression.

However, irrespective of the severity of depression, the scalability and low-resource implication of i-CBT make it ideal for use with or without guidance and support, and it is especially helpful in settings where there is high demand and long waiting times,[143] or where there are barriers to accessing outpatient services.[144] Furthermore, i-CBT is well received in terms of patient satisfaction and achieves good clinical outcomes,[145] although the real-world effectiveness of these results is difficult to parse due to the challenge of generalising findings from clinical trials to the general population.[145,146] Although i-CBT has received ample attention, and other internet-based psychological interventions are yet to be thoroughly examined, future research will probably reveal that such interventions can also be delivered effectively using digital health technologies.[147] For example, similar to i-CBT, guided internet behavioural activation therapy is effective and superior to treatment as usual and psychoeducation in the treatment of less severe depression, and is no different to other behavioural therapies and mindfulness, and it can also be used adjunctively.[148]

Psychological management strategy

A systematic approach should be adopted for psychological interventions. For less severe depression, specific psychological treatments can be prescribed as well as non-directive counselling and supportive therapy, and in many cases, offering psychological therapies in group settings might suffice.[149] In contrast, in more severe depression, preference should be given to individual therapies of greater intensity that target the specific symptom profile of patients (table 1).[151,152] In addition to recognised psychological interventions such as CBT and interpersonal therapy,[131] non-specific, non-directive psychological strategies and supportive therapies such as counselling that alleviate stress will probably benefit patients who are reasonably well between episodes.[153]

Antidepressants

Over 30 different antidepressants can be used to treat depression. They are usually prescribed by physicians, and their availability varies across different jurisdictions and health systems around the world. Having displaced tricyclics, which dominated during the 20th century,[154] SSRIs are now the most widely prescribed antidepressants for the treatment of depression,[155–158] and this shift towards newer medications has been accompanied by an increase in antidepressant prescriptions, which has made the management of depression more costly.[159]

Antidepressant prescription requires careful deliberation of several factors, beginning with whether the patient wants to take medication[160] and how well they cope with adverse effects should they occur, as tolerability affects medication adherence throughout management (appendix p 7).[160,161] Therefore, the administration of antidepressants, especially their commencement, should take place in an established therapeutic relationship and might require psychiatrist involvement. Importantly, transient adverse effects might occur upon initiation of antidepressant treatment, such as headache, nausea, or gastrointestinal issues (figure 3), which typically cease within a week. However, if these symptoms persist, are severe, and/or are accompanied by other adverse effects, a treatment review is warranted to consider potentially withdrawing or switching the medication.

Antidepressant choice

Numerous factors can influence antidepressant prescribing choice,[171] but the selection of an antidepressant should be based on patient characteristics, illness features, access to treatment, and its pharmacological properties, as well as medication history and whether any comorbidities are present. Patient characteristics such as age and gender are important due to interindividual biological variability in antidepressant distribution and metabolism,[172,173] which play a crucial role in determining clinical response and the occurrence of adverse effects (table 3). Alongside these, it is also important to consider illness features that define the person's depression such as symptom profile and illness severity. In practice, balancing the

	Focus and core elements
Cognitive behavioural therapy	Identifies, challenges, and interrupts negative cognitions
Behaviour therapies, including behavioural activation	Increases engagement in activities that provide pleasure, and a sense of accomplishment
Interpersonal therapy	Improves unhelpful relationship patterns or situations
Psychodynamic psychotherapy	Explores unconscious motivations and unresolved conflicts and how these affect emotions, cognitions, and behaviours
Problem-solving therapy	Identifies problems and develops strategies and skills to successfully manage them
Schema-focused therapy	Changes long-held, self-defeating thought patterns and beliefs
Metacognitive therapy	Decreases perseverative thinking processes and metacognitions such as worrying, rumination, and uncontrollability of thoughts
Acceptance and commitment therapy	Acceptance of undesirable life experiences and difficulties and development of psychological flexibility to adapt to them
Dialectical behavioural therapy	Developing mindfulness, distress tolerance, interpersonal effectiveness, and adaptive emotion regulation
Rational emotive behaviour therapy	Replaces irrational beliefs with rational beliefs to reduce distress and increase functioning
Mindfulness-based therapies, including cognitive therapy	Enhances awareness of feelings, thoughts, and situations to reduce automatic responses
Positive psychotherapy	Increases positive emotions, engagement, and personal strengths
Counselling or non-directive support (non-manualised approaches)	Helps people find their own solutions by listening and empathising

An overview of psychological interventions for depression, highlighting their distinctive core elements.[25,150] For further information, including detailed definitions and specific examples of each of these therapies and evidence supporting these interventions, see the appendix (pp 8–11).

Table 1: **Major psychological interventions for depression**

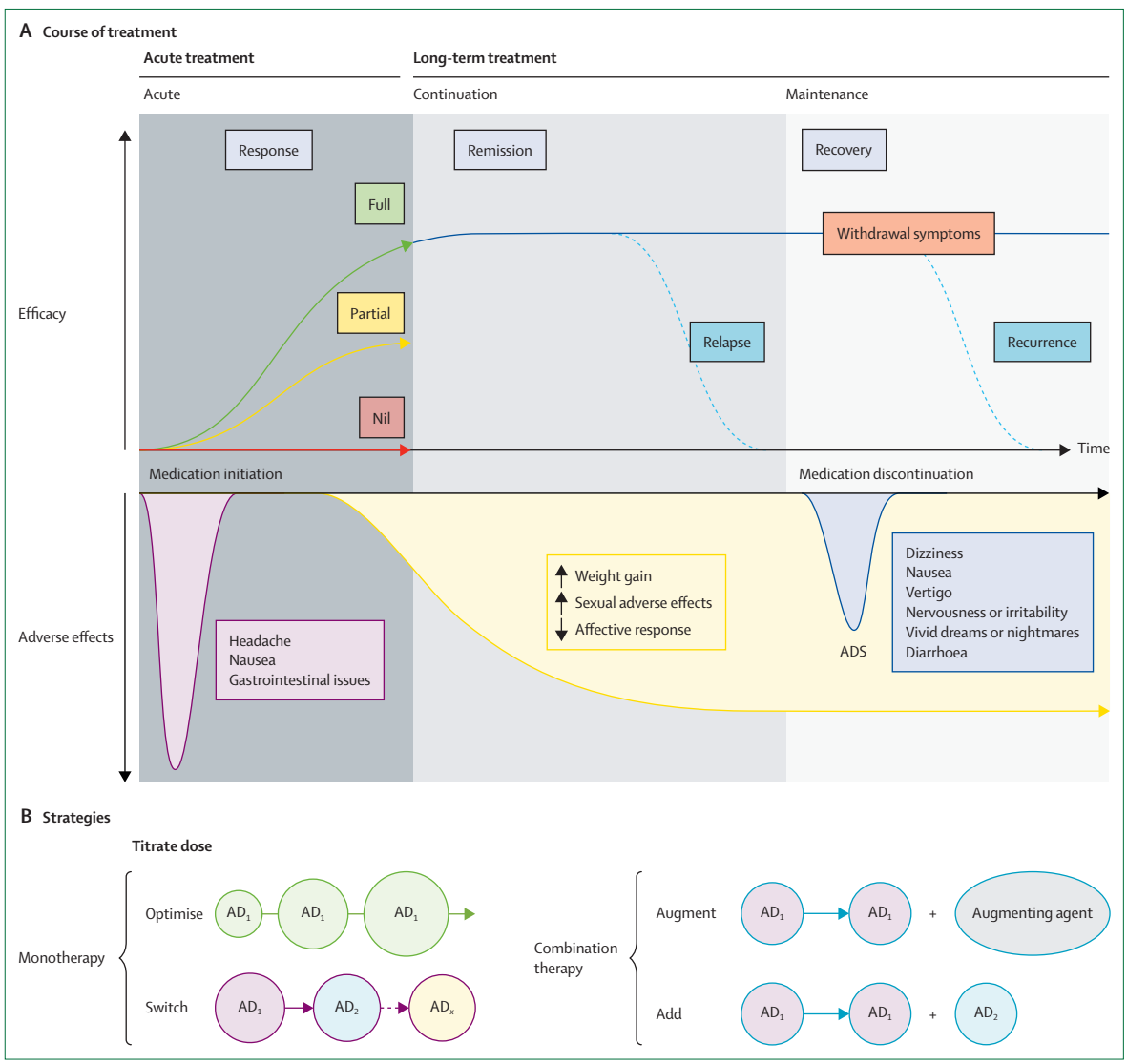

Figure 3: **Framework for pharmacotherapy of depression**

(A) Course of treatment. The treatment of depression comprises three phases: acute, continuation, and maintenance. These are demarcated by remission and recovery. Medication initiation: when initiating an antidepressant, potential acute and chronic adverse effects should be discussed. Medication discontinuation: the withdrawal of medication has a risk of both ADS[162] and relapse or recurrence (table 2; panel 2).[164] If symptoms recur on withdrawal of an antidepressant and ADS is ruled out, further ongoing treatment might be needed and medication could be reintroduced. (B) Strategies for ongoing treatment. Beginning with initiation and then optimising and combining or switching as necessary. Overall, there are two approaches—monotherapy or combination therapy. Monotherapy is preferable as it simplifies management and it is clearer which agent is responsible for a response or adverse effects. Prescribing only one agent also minimises adverse effects. If a response is only partial then combination treatment can be considered: several strategies can be used to enhance a partial response to AD_1, including augmenting with lithium or atypical antipsychotics such as quetiapine or aripiprazole,[165,166] or adding another antidepressant (eg, combining mirtazapine with venlafaxine). Combination therapies are only indicated if AD_1 has produced a reasonable partial response.[44] In real-world practice, most clinicians tend to switch to another antidepressant and this has the advantage of maintaining monotherapy.[56] Furthermore, the pattern of switching varies considerably but over a series of three antidepressant switches, the general trend seems to be switching from SSRIs to other medications such as mirtazapine, SNRIs, and tricyclics. SSRIs remain the most popular option throughout, despite a decrease in their overall use across successive trials. In contrast, mirtazapine use appears to remain steady and the use of other agents such as SNRIs and tricyclics gradually increases.[167] When switching antidepressants, within-class switching is recommended because of poor tolerability. However, if switching because of inefficacy, then trialling an altogether different molecule (from a different class with a different mechanism of action) is perhaps advantageous.[168] The STAR*D study,[169] a prospective trial of more than 4000 patients with depression reported that the cumulative remission rate after up to four antidepressant treatment trials was 67%, although this has been challenged recently by a re-analysis, which suggested that the rate should be 35%.[170] Either way, there are a substantial number of patients that do not respond to pharmacotherapy, underscoring the need for a multifaceted approach that combines antidepressant treatment with psychological interventions and includes foundational lifestyle modifications. AD_1=antidepressant 1. AD_2=antidepressant 2. AD_x=antidepressant x. ADS=acute discontinuation syndrome. SNRIs=serotonin–norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors.

benefits of treatment against potential costs along with consideration of patient preferences usually helps decide which antidepressants are suitable. Another important consideration is the treatment setting (eg, hospitals, specialist outpatient centres, primary care, or within the community) as this affects the ability to monitor treatment. However, all these important considerations are only pertinent if a medication is available and can be readily accessed.

Beyond knowing whether a particular antidepressant is effective, its specific efficacy is not an important factor when deciding treatment choice. This is because, compared with placebo, most antidepressants are equally efficacious.[42,180] The reason for this homogeneous effect is not fully known, but it might be a consequence of antidepressant mechanisms converging downstream, both intracellularly and functionally (eg, within neural networks). Furthermore, in real-world primary care settings, antidepressants only achieve small-to-medium effectiveness with moderate-to-high tolerability and low acceptability.[181] Consequently, SSRIs are the most commonly prescribed first-line agents irrespective of severity and setting,[155] whereas prescription patterns of other antidepressants vary.[156,171] This is because SSRIs are generally better tolerated and safer than most other antidepressants, particularly older agents (appendix p 7).[155,156,182]

In recent clinical guidelines, recommendations about antidepressant choice are based on depression severity, rated broadly as less or more severe (as per the UK National Institute for Health and Care Excellence guidelines),[25] or clinical factors such as efficacy and tolerability (eg, the Royal Australian and New Zealand College of Psychiatrists guidelines),[44] and medication options are sequenced as first-line, second-line, and third-line (eg, the Canadian Network for Mood and Anxiety Treatments).[42] However, grading severity is not necessarily or always informative,[180] and clinical symptom profiling might not meaningfully inform treatment choice.[183] Furthermore, many contemporaneously published guidelines for managing depression advocate different approaches and position different antidepressants as first-line therapy, which suggests that the evidence does not definitively support superiority of any one strategy over another, and that in clinical practice, perhaps considering elements from all three approaches (lifestyle, psychological, and pharmacological) is apt (figure 1).

Acute treatment: initiating antidepressant therapy

The pharmacotherapy of depression comprises three phases (acute, continuation, and maintenance) that are separated by transitions (ie, remission and recovery). Therefore, continuation and maintenance refer to long-term treatment that includes antidepressant discontinuation.

When commencing antidepressants, they should be prescribed at a third to a half of the recommended

	Features
Relapse	Recrudescence of same disorder episode due to loss of pharmacological effect
Recurrence	New episode of depression following previous recovery (remission over 6–9 months) due to loss of pharmacological effect
Rebound	Re-emergence of primary disorder symptoms to a greater extent than before taking medication; greater risk of relapse compared with patients not receiving antidepressants
Acute discontinuation syndrome	Non-specific symptoms (influenza-like, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal); onset soon after discontinuation; transient and self-limiting in duration; quick improvement in symptoms upon resumption of medication

Adapted from Henssler et al (2019).[163]

Table 2: **Differential diagnosis of symptoms that follow antidepressant discontinuation or dose reduction**

	Preferred antidepressant(s)
Demographics	
Age	
Adolescents*	Fluoxetine or escitalopram[174,175]
Older adults	Trazodone[176]
Gender	
Pregnancy	SSRIs (citalopram, fluoxetine, sertraline, and escitalopram are most common)[171,177]
Menstrual disorders	Paroxetine, venlafaxine, or sertraline[178]
Clinical factors	
Symptoms	
Anxiety	SNRIs or SSRIs
Cognitive difficulties (eg, learning, memory, and decision making)	Duloxetine or vortioxetine
Sleep disturbances (eg, insomnia)	Agomelatine or mirtazapine
Fatigue	Bupropion
Pain	Duloxetine or tricyclics
Melancholia (eg, psychomotor slowing and diurnal mood variation)	Tricyclics
Psychotic symptoms (eg, mood congruent delusions)	Antipsychotic medication in addition to antidepressants
Atypical symptoms (eg, increased sleep and increased appetite)	Monoamine oxidase inhibitors
Loss of weight or anorexia	Mirtazapine[179]
Lifestyle factors	
Substance use	
Tobacco dependence	Bupropion
Opioid dependence	Doxepin

In addition to the two major classes (tricyclics and SSRIs), agents with broader monoaminergic actions than SSRIs but with better tolerability than tricyclics are available, in addition to those that are thought to act via different (ie, non-monoaminergic) pathways. These additional properties are thought to lend antidepressant medications suitability for different clinical profiles.[25,44,171] However, evidence to support differential efficacy according to clinical profile is absent, and in practice, management decisions should be based on tolerability and safety as well as efficacy. Nevertheless, by virtue of their properties, some agents have additional uses, and antidepressant effects that are seemingly adverse might at times be desirable. For example, sedation and weight gain might be helpful in patients with insomnia and those who are underweight because of depression. Many antidepressants also have anxiolytic effects (eg, SSRIs), although when first prescribed they can worsen anxiety. SSRIs=selective serotonin reuptake inhibitors. SNRIs=serotonin–norepinephrine reuptake inhibitors. *For important advice regarding prescription of antidepressants in adolescents, see panel 7.

Table 3: **Pharmacotherapy of depression based on clinical profile**

Panel 7: Risk of suicide and antidepressants

The risk of suicidality (suicidal thinking or behaviour) is increased in adolescents and young people. Therefore, in the USA, many agents carry a US Food & Drug Administration black-box warning. In the UK, the safety warning from the Medicine and Healthcare products Regulatory Agency states that suicidal acts and behaviour are increased with the use of selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors in people younger than 25 years, and that the risks for specific antidepressants outweigh the benefits. Therefore, these antidepressants should not be used in this patient age group.

Consequently, routine monitoring of suicide is recommended in patients receiving antidepressant treatment, particularly at the outset (for the first 4 weeks or so) following the initiation of a new medication, and also after stopping treatment, and this message should also be included in any psychoeducation that is provided.[20,51]

Panel 8: Antidepressant discontinuation syndrome

Symptoms

- Mainly mild, reversible, non-specific, and physical in nature
- Peak: 36–96 hours
- Rapid onset within 1 week of discontinuation (3–5 half-lines)
- Resolve
  - Spontaneously (usually within 2 weeks), but might take longer (up to 6 weeks) depending on half-life
  - If medication is resumed

Risk for individual antidepressants

- Very high: phenelzine and tranylcypromine
- High: tricyclic antidepressants, venlafaxine, desvenlafaxine, and paroxetine
- Moderate: sertraline, citalopram, escitalopram, duloxetine, and vortioxetine
- Low: fluoxetine and milnacipran
- No risk: agomelatine
- Unclear or unknown: mirtazapine and bupropion

Adapted from Henssler et al (2019).[163]

therapeutic dose (appendix pp 5–6) and then gradually increased over 1–2 weeks to minimise the likelihood of adverse effects.[55] This is because if adverse effects occur, patients might stop taking their medication and typically antidepressants take several weeks to produce discernible clinical improvement. Therefore, when commencing antidepressants or altering dose, a frank discussion of likely outcomes and the risks involved is essential, and regular follow-up and monitoring should be instituted.[44] Additionally, patients should be aware that more than one antidepressant might need to be tried to achieve a satisfactory and sustained response; there are many different antidepressants available, each with unique actions and tolerability profiles; and in most cases depression resolves with treatment.[184] However, knowing which antidepressant will work is largely contingent on trialling the medication, because in community settings, prediction based on baseline characteristics alone has limited accuracy.[185] Therefore, measurement-based care, including mood monitoring for example, and systematic outcome assessment are important, as early response to treatment remains a useful clinical indicator of eventual outcomes.[186] Of those that respond poorly to an antidepressant, 35–67% of patients are likely to eventually improve if an alternative strategy is adopted, such as switching to another antidepressant, adding another medication, or adding or switching to a psychological intervention.[169,170]

In the management of depression, the initial few weeks before and after starting any treatment is a high risk period for suicide, and although antidepressants generally reduce suicidal ideation, a small proportion of patients, especially young people, might experience increased suicidal ideation when initiating antidepressant therapy (panel 7).[10,50]

Continuation and maintenance phase: long-term treatment

The treatments prescribed for an acute episode of depression will probably be continued into maintenance therapy, and therefore many of the same considerations (eg, tolerability and antidepressant response that apply at the outset) remain relevant throughout the course of long-term treatment (figure 3).[187] To be confident of preventing relapse, continuation and maintenance treatment should jointly last for at least 6–9 months and ideally a year.[55,151] Once a person has fully recovered, antidepressant treatment should be gradually withdrawn—slowly tapering medication dosage accompanied by structured psychological support.[188] However, stopping antidepressant therapy is not straightforward and discontinuation of antidepressant treatment requires careful planning and close monitoring, especially since a third of patients who discontinue treatment will have discontinuation symptoms,[189] and as many as one in 30 cases might be severe (figure 3; panel 8; table 2).[190]

Non-response and treatment of depression in different populations

Management of depression in adolescents[10] and older adults,[191,192] as well as the needs of managing peripartum depression[42,193,194] and depression occurring in the context of physical diseases,[195] require additional considerations that are beyond the scope of this Seminar. In many of these contexts, outcomes are poor, which is a problem that affects depression more generally[17,196] and is being researched within the concept of treatment-resistant depression.[197–200] In each of these

Panel 9: Complementary treatments and emerging therapies

Complementary treatments

Complementary treatments include herbal compounds and nutraceuticals. Inconsistency of therapeutic dose ranges for most complementary treatments and lack of sufficient evidence, which is on par with that for antidepressants and psychological interventions, means that they are only recommended for treating less severe depression, but can be used adjunctively for more severe depression.

Herbal compounds include St John's Wort, saffron, lavender, and roseroot. Of these, only St John's Wort has evidence of efficacy in less severe depression. Hence, they are positioned as third-line treatments in the Canadian Network for Mood and Anxiety Treatments' guidelines.[42] Similarly, nutraceuticals (unregulated substances derived from natural sources), including dietary supplements and food additives such as omega-3 fatty acids and dehydroepiandrosterone, are regarded as second-line or third-line treatments for depression.

Emerging therapies

In recent years, renewed interest in developing novel treatments for depression has been fuelled by increasing frustration with existing therapies. Almost a third of patients with depression have a poor response to at least two adequate courses of currently available antidepressants and are referred to as treatment-resistant. As most antidepressants act on monoaminergic pathways, alternative mechanisms of action have been sought, often with the additional aim of having more immediate impact.

Ketamine and esketamine

Ketamine is an established dissociative anaesthetic that has been found to have psychoactive properties at subanaesthetic doses.[203] Binding to glutamate receptors, ketamine and its s-enantiomer (esketamine) reduce the symptoms of depression and suicide thoughts.[204,205] As such, intravenous ketamine is already used in the UK National Health Service to treat severe depression as an alternative to electroconvulsive therapy (appendix p 19).[206] However, even though the administration of intranasal esketamine and oral ketamine is easier, their use is limited partly due to limited long-term effects and the risk of dependence, but also due to the high cost of esketamine.[207] Hence, the National Institute for Health and Care Excellence does not endorse its use, and the US Food & Drug Administration has only approved esketamine as an adjunctive therapy to be administered alongside an oral antidepressant. A similar combination of ketamine with psychotherapy for depression is also available in the USA and the UK but this is not evidence-based.

Brexanolone

Brexanolone is a neurosteroid that structurally resembles endogenous allopregnanolone. It is a GABAergic system neuromodulator that enhances GABA signalling, a reduction in which has been found in women at risk for postpartum depression. Clinical trials have found it to be effective in this population and therefore it has an indication for postpartum depression (appendix pp 12–13).[208] Zuranolone—an allosteric GABA receptor modulator—is also showing antidepressant potential in early clinical trials.[209]

Medicinal cannabis

Components of *Cannabis sativa* are thought to have therapeutic potential and, in jurisdictions where medicinal cannabis products are licensed,[210] these are increasingly being self-administered to treat a range of medical and psychiatric conditions.[211] Although the main use of medicinal cannabis is for chronic pain, anxiety, sleep disorders, and post-traumatic stress disorder, individuals with depression are also taking specific formulations.[211] However, although there is some preliminary evidence regarding the use of medicinal cannabis in anxiety,[212] the evidence for its use specifically in depression is scarce (ie, its use to treat depression is not evidence-based). This is probably because, of the several hundred compounds within cannabis, tetrahydrocannabinol and cannabidiol are the most common, and while tetrahydrocannabinol is psychoactive (ie, causes a high), cannabidiol is not. However, in practice and especially in jurisdictions where there is no regulation of medicinal cannabis-containing products, those that are labelled as cannabidiol might contain tetrahydrocannabinol and might not be accurately labelled. Hence there is potential for substantial misuse of medicinal cannabis (appendix pp 12–13).[213,214]

Psychedelics

Psychedelics have a long history of use in healing as well as in ceremonies of religious and spiritual importance. A resurgence of interest in the past two decades has brought several agents to the fore, many of which are administered alongside psychotherapeutic interventions.[215,216]

Psilocybin is found in specific species of fungi and is consumed orally in the treatment of depression alongside psychological support.[217] Recent research suggests it might have some benefit in select cases, but emerging evidence also points to a potential increase in suicidality.[218] Hence, it is only available under supervision in approved health-care settings (appendix pp 12–13).

Ayahuasca is a traditional Amazonian plant medicine that is brewed to extract the hallucinogen dimethyltryptamine. Preliminary randomised controlled trials suggest a rapid but very short-lived antidepressant effect, with the majority of those injecting ayahuasca vomiting and many having severe nausea (appendix pp 12–13). Other molecules currently being investigated for their use in psychiatric disorders include 3,4-methylenedixoymethamphetamine (MDMA; also known as ecstasy). Currently MDMA has only been licensed for use in the

(Continues on next page)

(Panel 9 continued from previous page)

context of MDMA-assisted therapy for the treatment of post-traumatic stress disorder, and there is currently no evidence for its use in the treatment of depression.[219]

Anti-inflammatory medications and agents

Minocycline is an established tetracycline antibiotic that treats a broad spectrum of bacterial infections, including acne. It has been trialled in the treatment of depression (treatment-resistant and comorbid) both as monotherapy and adjunctive to antidepressants, and has been found to have variable benefit.[220–222] It is well tolerated but further research to establish its therapeutic profile as an antidepressant is under way.

Neuropeptide Y is produced in neurons and is involved in physiological regulatory processes including inflammatory mechanisms implicated in depression. When administered intranasally alongside an antidepressant, it appears to produce a rapid antidepressant effect that is short-lived.[223] Although promising, as it builds on the inflammatory hypothesis of depression, further research is needed.

Celecoxib—a non-steroidal anti-inflammatory drug used commonly for arthritic pain—has been found to have an antidepressant effect when prescribed adjunctively.[224]

Omega-3 fatty acid and cholesterol-lowering statins have been found to be effective when administered alongside antidepressants in treating depression, and omega-3 fatty acids are also useful as monotherapy; however long-term benefits need further research.[224]

Probiotics that contain live microorganisms have been investigated for antidepressant effects based on the hypothesis that gut alterations in microbiota can affect mental illnesses via gut–brain communication. Specific probiotic strains appear promising and might work by modifying the production of neurotransmitter precursors in the gut and countering inflammatory processes.[225] Similarly, prebiotics that consist of non-digestible fibre that stimulate gut bacteria selectively might also be of benefit in treating depression; however further research is needed.

Microbiome-targeted therapies

Faecal microbiota transplantation involves the transfer of faecal matter from a healthy person into the digestive system of a patient with depression. The aim is to restore the microbial composition of the gut. The process of faecal microbiota transplantation has shown encouraging results but further research is needed to understand the relationship between gut bacteria and depression and how altering the gut microbiota can alter mood.[226–228]

clinical situations, the diagnosis and management of depression must be tailored and is best informed by additional guidance that is specific to population needs.[201,202]

In addition to the established treatments and mainstream management strategies discussed in this Seminar, there are many novel complementary and innovative interventions for the treatment of depression that are under investigation and initial findings appear promising, although evidence to date for these interventions is weak. However, a detailed discussion of these new and emerging therapies is beyond the scope of this Seminar, especially as many have limited availability. As patients might ask about these interventions, their potential uses are summarised in panel 9, and further information is available in the appendix (pp 12–13).

Conclusion

Depression is common throughout adulthood, and psychoeducation, lifestyle modifications, and psychological interventions might help anticipate acute exacerbations and limit illness duration. Treatments for depression are as multifaceted as the illness itself. A large proportion of patients will require multiple treatments to regain normal functioning, some will require referral to specialists and hospitalisation, and a few might never fully recover. Therefore, research into the development of new medications remains crucial alongside improving diagnosis and management using existing knowledge and treatments.

Contributors

GSM, EB, and VK conceptualised the Seminar and developed the figures. All authors contributed to the literature search, writing of the original draft, and subsequent writing, reviewing, and editing.

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