Comorbid depression in medical diseases

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Abstract | Depression is one of the most common comorbidities of many chronic medical diseases including cancer and cardiovascular, metabolic, inflammatory and neurological disorders. Indeed, the prevalence of depression in these patient groups is often substantially higher than in the general population, and depression accounts for a substantial part of the psychosocial burden of these disorders. Many factors can contribute to the occurrence of comorbid depression, such as shared genetic factors, converging biological pathways, social factors, health behaviours and psychological factors. Diagnosis of depression in patients with a medical disorder can be particularly challenging owing to symptomatic overlap. Although pharmacological and psychological treatments can be effective, adjustments may need to be made for patients with a comorbid medical disorder. In addition, symptoms or treatments of medical disorders may interfere with the treatment of depression. Conversely, symptoms of depression may decrease adherence to treatment of both disorders. Thus, comprehensive treatment plans are necessary to optimize care.

Major depressive disorder (MDD) is a very common disorder with a point prevalence of ~1 in 20 individuals and a lifetime risk of ~1 in 6 individuals, globally[1]. Although the prevalence varies by region and country, depression is common in all parts of the world, making it one of the leading causes of years lost to disability worldwide[2]. Depression is particularly common in patients with a medical illness; indeed, risk of depression is elevated several-fold in many of these patient populations compared with the general population. This increased risk includes MDD, the diagnostic entity of depression, as well as depressive symptoms below the diagnostic threshold for MDD. In this Primer, we use 'MDD' to refer to the formal diagnosis, 'depressive symptoms' for subthreshold depression, and 'depression' when both are included or in more general statements.

Comorbid depression has pronounced clinical implications as there is an additive or even synergistic negative effect of depression and chronic medical diseases on overall health[3]. Importantly, comorbid depression often negatively affects patients' quality of life (QOL)[4], further adding to disease burden. The effect of comorbid depression on overall QOL varies depending on the characteristics and treatment of the medical disorder, resources available to the patient and the severity of the depression. Moreover, depressive symptomatology is associated with decreased adherence to medical treatments, such as in patients with diabetes mellitus[5] or brain tumours[6], and is associated with a higher risk of receiving non-guideline medical treatment in women with breast cancer[7]. Importantly, comorbid depression has also been associated with worse prognosis and increased mortality in many medical diseases[8–10]. Moreover, mental disorders, including MDD, increase the risk of developing a wide range of medical disorders later in life[11], with potential implications for morbidity and mortality. Indeed, a nationwide study in Denmark showed that mental disorders are associated with excess life-years lost for medical disorders[12]. Of note, suicide is not a major driver of this effect and its relevance for increased mortality in patients with comorbid depression seems to be decreasing[12,13]. In addition, an umbrella review[14] demonstrated nominally significant associations between MDD and increased mortality in all assessed settings and populations. However, whether or not there is a causal effect of depression on mortality is debated[15].

Several mechanisms could underlie the co-occurrence of depression and a medical disease, ranging from biological processes to treatment-induced morbidity, behavioural links and psychological factors (FIG. 1). In addition, social factors may affect the risk of developing depression as well as chronic medical diseases (BOX 1). Of note, the possible explanations for the co-occurrence of two diseases, particularly if both are common diseases, always

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include chance. Models of the association between depression and medical diseases (FIG. 1) are hypothetical heuristics and, in any given patient, a mix of these pathways usually contributes to the development of depression.

This Primer provides a broad overview of the prevalence, pathogenesis, diagnosis and treatment of comorbid depression in patients with a wide range of chronic medical disorders. To keep the summary informative, this Primer focuses on more common medical disorders and is restricted to chronic, non-communicable illnesses. Certain diseases are highlighted in each section where the topic is — in our opinion — particularly relevant or illustrative. In many instances, overviews that expand on the specific considerations in any given medical disease are referenced. The main focus of the Primer is on MDD rather than depressive symptoms; however, as subthreshold depressive symptoms can have pronounced health implications, some references on this topic are included throughout. Priority was given to evidence from large population-based or cohort studies, large randomized controlled trials (RCTs) and meta-analytic evidence wherever available. In some instances, smaller studies or animal models are cited if they illustrate a crucial point, particularly in terms of mechanisms or treatments.

Epidemiology

The prevalence of MDD in the general population is ~5%[16,17], with a lifetime risk of ~15%[18]. MDD is more frequent in women than in men[18,19], in people aged >75 years than in younger people[20,21] and in those with medical diseases than in those without[22,23]. An estimated 12% of general hospital inpatients have comorbid MDD[22] and an estimated 27% of general outpatients have depression or depressive symptoms[23] (FIG. 2).

Meta-analyses of the prevalence of MDD in patients with chronic medical diseases that are cited below often included studies with considerable heterogeneity regarding severity, stage and duration of the medical diseases and used different depression instruments (such as self-rated or clinician-rated). Of particular importance, the studies varied regarding the timing of assessment of comorbid MDD prevalence, ranging from the point prevalence to the prevalence within 12 months or >1 year after the onset of the medical disease. Differences in MDD prevalence in relation to the reference time period were analysed for few diseases (for example, stroke), whereas most of the meta-analyses pooled a mean prevalence based on all included studies. For example, a study on the prevalence of MDD among hospital inpatients found a mean prevalence of 12%, ranging from 5% to 34%[22]. Although potential differences are discussed below, a detailed description of this heterogeneity is beyond the scope of this Primer (see REFS[16,17] for an in-depth discussion of these aspects) and, therefore, the rates given are approximate.

Cancer

The point prevalence of comorbid MDD in one meta-analysis of studies applying diagnostic interviews among patients treated in oncological or haematological settings was 16.3%[24]. A similar rate of 16.5% was found in palliative care settings[24]. One meta-analysis included studies that used diagnostic interviews and self-report instruments and found a prevalence of 14% when diagnostic interviews were used, with a prevalence of 7–24% with self-report instruments[25]. In this study, comorbid MDD was more prevalent in patients <60 years of age, women and those with worse deprivation[25]. In addition, MDD was more prevalent during treatment (with a prevalence of 14% with diagnostic interview and 27% with self-report instruments) than <1 year after treatment (a prevalence of 9% and 21%, respectively) and ≥1 year after treatment (a prevalence of 8% and 15%, respectively)[25]. In accordance with these data, differences in the prevalence of MDD by treatment status have been found in other studies, such as a prevalence of 17.3% before treatment, 14.7% during treatment and 18.4% after treatment in patients with prostate cancer[26], and 25.3%, 23.0% and 12.7%, respectively, in those with ovarian cancer[27]. Collectively, these data indicate that the prevalence of MDD may be higher during active disease than during remission. However, other studies have found no difference in comorbid MDD prevalence in patients receiving initial cancer treatment, or whether the initial treatment objective was palliative or curative; there was insufficient data to examine cancer stage or type of cancer treatment[24,25].

Although comparisons across studies are difficult owing to methodological differences, the prevalence of comorbid MDD has been estimated to be particularly high in patients with ovarian[27] or brain tumours[28]. Indeed, one large cross-sectional study in Germany in patients with major cancer types found the highest prevalence of mood disorders in patients with breast tumours, in women with tumours of the reproductive system and in patients with kidney tumours[29]. The reason for these differences remains unknown but may be related to tumour site, sex, multimorbidity, social status, treatments, time since diagnosis, or pain and fatigue

severity. An increased risk of MDD in adulthood has been found among those who had cancer during childhood, although, in general, research into the prevalence of depression in paediatric cancer populations is limited[30].

Cardiovascular diseases

The prevalence of MDD in patients with heart failure ranges from 11% in those with New York Heart Association defined class I heart failure to 42% in those with class IV[8], with one study suggesting that patients <60 years of age are more vulnerable to depression than older patients[31]. A similar prevalence range (3–48%) has been found in patients with peripheral artery disease, with a higher prevalence in those with more severe symptoms[32]. In addition, ~28% of patients with myocardial infarction have comorbid MDD[33], of which depression is more frequent in women than in men, patients with anterior myocardial infarction, comorbid hypertension, a history of previous myocardial infarction compared with first-time infarction, or comorbid diabetes mellitus[33,34]. In accordance with these data, another meta-analysis found a higher frequency of comorbid MDD among women with myocardial infarction, compared with men, although a lower left ventricular ejection fraction (indicating an increased severity of infarction) was associated with higher depression scores among men only[34].

Metabolic diseases

The estimated prevalence of comorbid MDD is 23% in men and 34% in women with type 2 diabetes mellitus[35], and 12% in people with type 1 diabetes mellitus[36]. In patients with type 2 diabetes mellitus, the prevalence is higher among those <65 years of age (31%) than among those ≥65 years of age (21%)[35]. Depressive symptoms are also frequent in young people <18 years of age with type 1 diabetes mellitus (30.04%)[37] and women with polycystic ovary syndrome (36.6%)[38].

Neurological diseases

The prevalence of post-stroke MDD based on diagnostic interview is 17.7% after a mean of 6.9 months following stroke, rising to 33.5% when also including depressive symptoms[39]. During the acute post-stroke period, the prevalence was 18.1% after a mean of 3.4 weeks[39]. A meta-analysis of observational studies found that almost one in three patients had depression at <1 month,

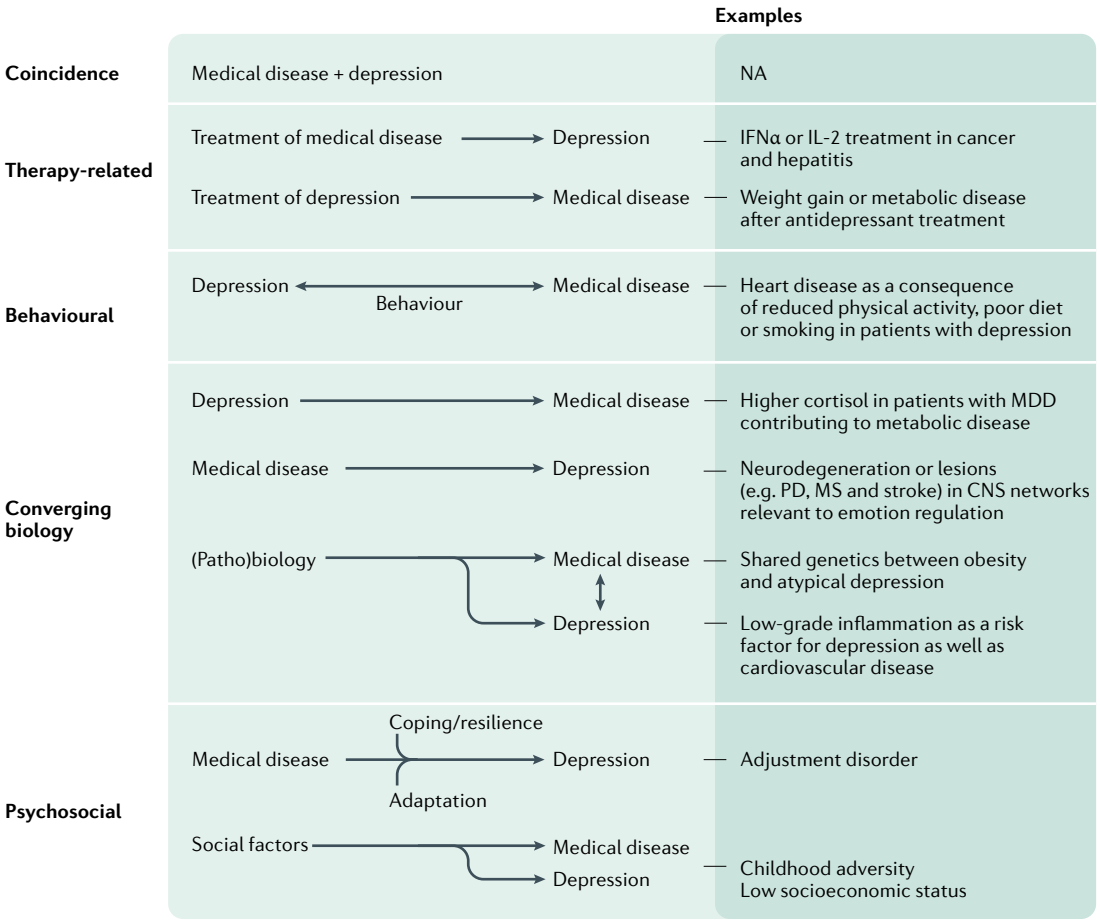

Fig. 1 | **Possible heuristic models to explain the comorbid occurrence of depression and medical diseases.** Several phenomena could link depression to a medical disease. These phenomena may include coincidence as well as several direct or indirect mechanisms such as therapy-related pathways, behavioural connections, converging biology and psychosocial factors. CNS, central nervous system; MDD, major depressive disorder; MS, multiple sclerosis; NA, not applicable; PD, Parkinson disease.

Box 1 | **Social determinants of mental and physical health**

Social and environmental factors have an important role in mental[278] and physical health[279]. A considerable body of evidence suggests that (psycho)social factors that are associated with an increased risk of depression are also associated with risk of chronic medical diseases such as cardiovascular disease or cancer. For example, adverse childhood experiences (such as maltreatment, interparental violence or parental drug use) are linked to a higher likelihood of mental and medical diseases later in life[280]. Many adult mental health conditions may actually initiate during adolescence, although there is limited research in this area[281].

Although the mechanisms of these overlapping associations are unclear, some evidence supports a role of potentially mediating effects of health-harming behaviours (such as smoking, physical inactivity or drug abuse)[282]. In addition, it is plausible that (psycho)social events such as adverse childhood experiences can directly alter biological systems including neurobiological circuits, endocrine regulation and immunological processes[283], which in turn may increase the risk of medical diseases in later life, particularly metabolic or cardiovascular diseases. Of note, low socioeconomic status is a well-established risk factor for higher morbidity due to behavioural factors (such as smoking and physical inactivity) and chronic diseases including diabetes mellitus and hypertension[284]. Similarly, depression risk also varies by socioeconomic status[285], although the association seems complex.

It is important to keep in mind that such epidemiological observations are likely to be driven by the combined effect of (psycho)social factors (such as childhood experience, educational attainment, employment and income), behavioural factors (such as diet and exercise), psychological (such as coping) and biological factors (such as genetics, epigenetics and neurobiological pathways), which are often closely intertwined. Of note, the direction of effects may go in both directions, that is, depression could negatively affect social factors such as education and income (drift hypothesis[286]). Ultimately, combining strategies will be required to reduce the risk and disease burden on an individual level and the societal level.

6 months, 12 months and >12 months after stroke[40]. Depression was more frequent following left hemisphere stroke and among patients with aphasia than in patients with stroke who did not have these characteristics[39].

In patients with multiple sclerosis (MS), the prevalence of MDD has been estimated to be 21%, with a prevalence of 35% in those with depressive symptoms[41]. One study found that, although women with MS have a higher risk of MDD than men with MS, the disparity in incidence between the sexes was lower for MS than in the general population[42]. Evidence from cross-sectional studies supporting a link between MS severity (measured by neurological disability) and depression risk is conflicting, but two large longitudinal cohort studies have suggested that comorbid MDD predicts faster subsequent progression of MS disability accumulation[43,44].

The prevalence of comorbid MDD in all patients with epilepsy was 21.9%, with a higher prevalence in women (26.4%) than in men (16.7%)[45]. In patients with Parkinson disease, the overall prevalence of MDD was 22.9%[46]. In patients with Alzheimer disease, the prevalence was 12.7%[47].

Inflammatory diseases

Meta-analyses have shown that the prevalence of comorbid MDD in patients with systemic lupus erythematosus[48], psoriasis[49], rheumatoid arthritis[50] and inflammatory bowel disease (IBD) is 15–25%[51]. The prevalence of depressive symptoms was 21.6% in patients with IBD[51], 28% in patients with psoriasis[49] and 38.8% in patients with rheumatoid arthritis[50]. In patients with rheumatoid arthritis, a higher prevalence of MDD was associated with lower age[50]. In patients with IBD, the prevalence of MDD was higher in those with Crohn's disease (25.3%) than in those with ulcerative colitis (16.7%), and was higher in patients with active disease (40.7%) than in those in remission (16.5%)[51].

Summary

Taken together, many medical diseases are associated with comorbid MDD with a prevalence of >10%, with several diseases showing estimates of >20%, meaning that the prevalence of MDD in those with chronic medical diseases is at least twice as high and often more than four times higher than the prevalence in the general population. The prevalence of subthreshold depressive symptoms is even higher than that of MDD. In some medical diseases, patients <65 years of age are more likely to develop depression[25,31,35], which may be due to the psychological aspect of having a severe and chronic disease at a young age. As highlighted above, associations between comorbid depression and severity, progression or activity of some medical disorders have been reported. However, more research is needed to determine whether specific subgroups of patients are particularly at risk of developing depression.

Mechanisms/pathophysiology

In many cases, the association between chronic medical disorders and MDD seems to be bidirectional in that the medical disorder increases the risk of depression and vice versa. A large number of potential mechanisms could account for this association (FIG. 3), and a complex interplay of many or all of these mechanisms probably underlies depression in a single patient. This section highlights a few of these putative mechanisms using illustrative examples of disorders that are particularly relevant.

Shared biology

Common genetic basis. The most obvious biological mechanism that could account for the comorbid occurrence of two disorders is genetic risk variants that are shared between the illnesses; several studies have used the increasing availability of large genetic datasets to address this question. Indeed, one association analysis explored the overlap between MDD genetic risk score and 925 disease outcomes in the UK Biobank dataset. The strongest associations were with other psychiatric disorders (such as anxiety), but associations were also found with ischaemic heart disease (OR 1.30, 95% CI 1.15–1.47) and hypercholesterolaemia (OR 1.22, 95% CI 1.12–1.34) as well as several inflammatory and haemorrhagic gastrointestinal disorders such as oesophagitis, non-infectious gastroenteritis, gastrointestinal haemorrhage and intestinal *Escherichia coli* infections[52]. A re-analysis of multiple genome-wide association study (GWAS) datasets also revealed some genetic overlap between psychiatric disorders and inflammatory diseases; however, for MDD, only an overlap with hypothyroidism persisted after adjustment for multiple tests[53].

More targeted studies in several independent large datasets of patients with depression and somatic illnesses have found robust evidence of a genetic overlap between obesity and MDD[54], in which higher polygenetic risk scores for higher BMI were associated with an increased

risk of atypical depression (characterized by weight gain or increased appetite; OR 1.18, 95% CI 1.12–1.25) but not the risk of depression without these symptoms (OR 0.96, 95% CI 0.93–0.99)[55]. Intriguingly, the patient group with atypical depression was also more likely to have a higher polygenetic risk score for high levels of inflammation (C-reactive protein (CRP)), providing a putative biological pathway for this association[55]. However, similar studies in related phenotypes including type 2 diabetes mellitus and glycaemic traits[56–58], or cardiovascular diseases (such as coronary heart disease[59]), have failed to yield convincing evidence supporting a genetic link with depression. Moreover, the genetic risk variants of psychiatric disorders (including MDD) and the most common neurological disorders (including MS, stroke, Parkinson disease, epilepsy and Alzheimer disease) are essentially non-overlapping according to a large GWAS including >1 million patients and healthy controls[60]. No convincing evidence has been published for genetic overlap between cancer and depression, although some candidate gene studies with small samples have been published[61].

(Neuro)biological overlap between depression and medical disorders. Shared (neuro)biological mechanisms could also underlie the relationship between MDD and chronic medical disorders and could occur before either disorder is diagnosed or could be part of the manifestation of the medical disorder that could increase the likelihood of depressive symptoms (or vice versa). Unsurprisingly, studied mechanisms and neurobiological and biological substrates have often included systems that have also been associated with MDD in general[1].

However, causality is difficult to infer in this area. Animal models of comorbid depression are difficult to establish because any induced medical disorder in mice (such as models of stroke or MS) may interfere with the behavioural assessments of 'depression-like' symptoms. However, there are a few notable exceptions, such as one study that demonstrated an inflammation-mediated causal relationship between obesity and anxiety or depression-like behaviour in mice that was independent of effects on weight[62]. This finding provides a translational link to the human genetics study that demonstrated an overlap between obesity and MDD, which also implicated inflammation[55].

In most cases, biological overlap between depression and medical disorders has been studied in cross-sectional and longitudinal cohort studies. To comprehensively review all case–control studies on biological substrates of depression in patients with medical disorders is beyond the scope of this Primer; accordingly, the discussion herein is focused on a few large prospective cohort studies, mostly conducted in cardiovascular disorders. For other disease areas, reviews of the literature are cited for the interested reader.

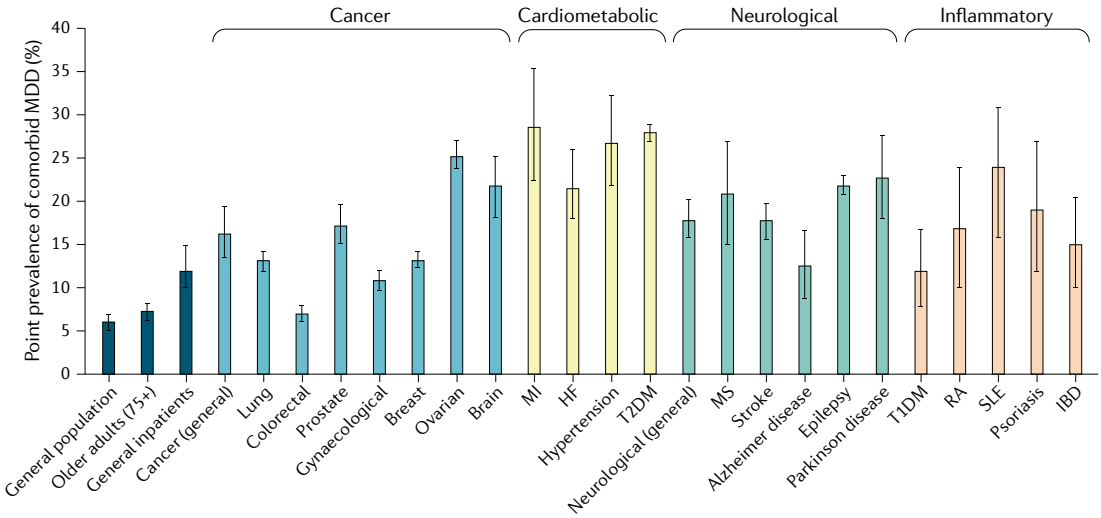

Fig. 2 | **Prevalence estimates of comorbid MDD in patients with chronic medical diseases.** The studies included in the meta-analyses showed a wide range of prevalence estimates with considerable heterogeneity reported, which could have been caused, for example, by the depression assessment instrument used, depression severity or duration of the medical disease. Hence, the values are considered approximate prevalence estimates of comorbid major depressive disorder (MDD), in which prevalence refers to the mean pooled prevalence calculated in the published meta-analyses for the specific medical diseases. Bars and error bars represent the prevalence of comorbid MDD and the 95% confidence intervals for each medical disease or disease group, respectively, as calculated in the individual meta-analyses of the general population[18,274], individuals >75 years of age[20], inpatients[22], and individuals with cancer (general)[24,25], brain cancer[28], breast cancer[275], prostate cancer[26], ovarian cancer [27], lung cancer, colorectal cancer and gynaecological cancer [276], myocardial infarction (MI)[33,34], heart failure (HF)[8], hypertension[277], type 2 diabetes mellitus (T2DM)[35], type 1 diabetes mellitus (T1DM)[36], stroke[39,40], multiple sclerosis (MS)[41], epilepsy[45], Parkinson disease[46], Alzheimer disease[47], systemic lupus erythematosus (SLE)[48], psoriasis[49], rheumatoid arthritis (RA)[50], and inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis[51]. Of note, 'cancer' includes data on several cancer types, people in palliative care or hospice settings and those who are not in palliative care, and patients with or without metastases. 'Neurological' includes data for MS, stroke, Alzheimer disease, Parkinson disease and epilepsy.

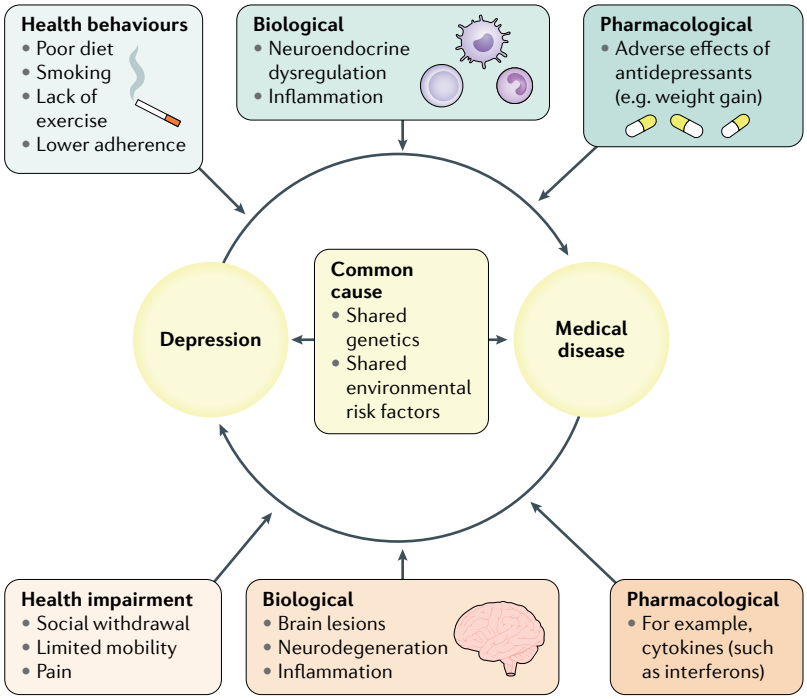

Fig. 3 | **Aetiopathogenesis of comorbid depression.** Shared genetic or environmental risk factors may contribute to comorbid depression in those with medical diseases. The link between depression and medical diseases could be enhanced via a bidirectional feedforward loop that includes behavioural, biological and pharmacological factors.

Increased activation and impaired feedback regulation of stress response systems such as the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) are amongst the best validated biomarkers for MDD onset[63]. Similarly, some evidence suggests that increased urinary noradrenaline[64] and cortisol levels[65] are associated with depressive symptoms in patients with coronary disease.

Inflammation has received increasing attention as an important biological substrate of depression, and elevated inflammatory markers including cytokines[66,67] and CRP[68], and signs of neuroinflammation including elevated cytokine levels (such as IL-6 and TNF) and an increased signal for translocator protein on PET imaging (which is thought to be a proxy of microglial activation[66,69]), in MDD in general have been confirmed by meta-analyses. Moreover, it is biologically plausible that inflammation represents a pathogenetic factor for depression, as animal models as well as experimental studies in humans have clearly demonstrated that inflammatory signals, especially cytokines, can temporarily induce depressive symptoms[70]. Thus, inflammation may contribute to the development of depressive symptoms in any medical disorder that has a pronounced inflammatory component in its pathophysiology. For example, in rheumatoid arthritis, numerous studies have implicated cytokines in the development of depressive symptoms (reviewed in REF.[71]), including clinical trials of drugs that specifically target cytokines such as IL-6 and IL-12/IL-23.

Indeed, a meta-analysis and a re-analysis of patient-level data from several published and unpublished RCTs have indicated that cytokine inhibitors (particularly anti-IL-6 and anti-IL-12/IL-23 therapies) may reduce depressive symptoms in patients with rheumatoid arthritis, Crohn's disease and other inflammatory disorders[72,73], suggesting a role for these cytokines in the pathophysiology of depression. These analyses have also suggested that this effect is — at least to some degree — independent of the effect of these drugs on the symptoms of the medical disorder (such as pain or functional capacity).

However, the relationship between immune function and depression in medical disorders is complex. For example, in the Heart and Soul study, depressive symptoms in patients with established coronary heart disease predicted subsequent increased levels of IL-6 and high-sensitivity CRP but the levels of these inflammatory markers at baseline did not predict depressive symptoms during the 5-year follow-up period[74]. Moreover, the observed relationships were strongly affected by health behaviours such as physical activity and smoking (see Behavioural links, below).

In addition, the immune system and the major stress response systems (HPA axis and the SNS) are closely linked in bidirectional regulatory circuits, which may be particularly relevant for depression in patients with metabolic disorders, such as diabetes mellitus. Indeed, numerous cross-sectional studies have shown that depressive symptoms in patients with type 2 diabetes mellitus correlate with inflammatory markers such as high CRP levels[75,76]. However, evidence for correlations between inflammatory markers and depressive symptoms in patients with type 1 diabetes mellitus is scarce (reviewed in REF.[77]).

Many studies have attempted to relate the location of tissue damage (that is, lesion pattern, neuroinflammation or regional neurodegeneration) in neurological disorders to the likelihood of a patient developing depressive symptoms or MDD. Several meta-analyses have found no evidence for an association between lesion location in stroke and the risk of developing depressive symptoms[78,79]. However, a connectome analyses of five independent datasets indicated that although lesions in post-stroke depression failed to map to a specific brain region, they mapped onto a brain circuit centred on the left dorsolateral prefrontal cortex[80]. Intriguingly, this circuit overlaps with non-invasive brain stimulation sites that may be effectively targeted for treatment of post-stroke depression[81]. In MS, neuroinflammation and regional neurodegeneration (particularly in circuits relevant to mood disorders including the hippocampus and connected frontotemporal networks) have been linked to depressive symptoms in case–control studies (see, for example, REFS[82,83]). This literature has been reviewed elsewhere[84].

Treatment-related mechanisms

Comorbidity of depression and medical disorders could also be related to (adverse) effects of drugs used for treating the medical disease or depression. Several drugs used for various medical disorders have been suspected to lead to depressive symptoms or even MDD, although this evidence stems from case reports and uncontrolled observational studies. For example, one comprehensive

survey of prescription records from 26,192 adults in the USA listed >200 drugs that were associated with a greater likelihood of concurrent depression[85]. However, in most cases, rigorous evidence for such associations or causal relationships is lacking. Furthermore, this list contained several antidepressants of different classes and anxiolytics such as benzodiazepines that are often used to treat depression. Thus, confounding by indication very likely plays a part in the association between these drugs and depression. Furthermore, for other medications, such as antihypertensive β-blockers, clinical experience suggests an association with depression, although this finding has not been supported by empirical evidence[86]. Some evidence suggests beneficial effects of statins in preventing and treating depression[87] owing to their pleiotropic effects, including anti-inflammatory effects, promotion of neuroplasticity, modulation of neurotransmitters and neuroendocrine function.

For drugs for which a causal relationship with depressive symptoms is plausible, potential mechanisms underlying medication-induced depression may include direct or indirect effects on the central nervous system (CNS) by modulating neurobiological systems that have been associated with depression such as the monoamine system, immune system and HPA axis. One of the examples with the most supporting evidence is immunotherapy (for example, IFNα or IL-2 injections)[88]. Indeed, up to 80% of patients treated with IFNα experience mood symptoms, often somatic or neurovegetative symptoms (such as fatigue, insomnia and reduced appetite) occurring within the first weeks of treatment[88]. In addition, one meta-analysis of observational studies estimated that 25% and 28% of patients treated with IFNα developed a major depressive episode after 24 weeks and 48 weeks, respectively[89]. Prior antidepressant treatment was associated with a reduced risk of MDD and lower depression scores[90]. Almost 80% of patients receiving IL-2 therapy experience fatigue[91], one of the frequent neurovegetative depressive symptoms, the proposed mechanism of which is its immune-activating effect[88]. These effects include direct and indirect signalling across the blood–brain barrier via active transport of the cytokines themselves, signalling via the vagus nerve and cellular pathways, where activated peripheral immune cells enter the CNS[88]. Such inflammatory signals from the periphery interact with neurotransmitters (such as serotonin via the kynurenine pathway), alter neuroplasticity, and promote excitotoxicity and oxidative stress[88]. Although confounding by indication may explain some cases, infusion of cytokines (for example, IFNα or IL-2) or endotoxin in healthy volunteers leads to depressive symptoms; this is one of the most robust human models of depression[92].

Behavioural links

Habitual aspects of lifestyle such as smoking, lack of physical exercise, excessive alcohol consumption and unhealthy diet contribute to a range of physical comorbidities and could, in part, mediate the influence of depression on physical disease risk and outcomes. At the same time, some health behaviours may reduce the risk of depression.

The prevalence of cigarette smoking and tobacco use is elevated among people with MDD compared with people without MDD. In addition, people with depression find it more difficult to stop smoking, and are at higher risk of relapsing following smoking cessation, than those without depression[93]. People with depression have greater nicotine dependence than those without depression, which underpins the maintenance of the habit[93]. As smoking is a well-established risk factor for certain cancers, cardiovascular diseases[94] and neurological disorders, including brain infarcts[95] and MS[96], it could at least in part contribute to the comorbidity. Of note, there is probably a two-way association between smoking and depressive symptoms. For example, longitudinal studies of adolescents have indicated that smoking predicts later increases in depressive symptoms, whereas depression in turn predicts smoking initiation[97]. These associations are important for physical comorbidities, as smokers with depression are less likely to stop smoking even when they have serious conditions such as chronic respiratory illness[98]. Population mortality studies have suggested that smoking explains a sizeable proportion of the excess mortality associated with depression[99].

Extensive research has linked physical inactivity with depression. Indeed, longitudinal studies have demonstrated that low levels of physical activity at baseline predict the incidence of future depressive symptoms for up to 10 years, and Mendelian randomization studies have suggested that this link is causal[100]. Conversely, people with depression tend to be more sedentary than those without depression, and this could increase the risk of several chronic disorders or have other health consequences. Importantly, the association between depression and adverse cardiovascular events in patients with coronary heart disease in the Heart and Soul study was largely explained by physical inactivity[101].

In addition, alcohol use disorder is strongly associated with the risk of MDD, with evidence suggesting that alcohol stimulates neurophysiological and metabolic changes that increase the risk of depression[102]. The connection between less severe alcohol consumption and depression is also well established, with heavy drinking that does not reach the levels of alcohol use disorder being associated with increased severity of depressive symptoms[101,102].

Another potentially relevant protective lifestyle factor is dietary composition. A number of longitudinal studies have shown that Mediterranean diets are associated with a reduced incidence of depression[103,104]. In addition, Mediterranean diets are also cardioprotective[105]. However, whether changes in diet could modify the relationship between depression and comorbidities is unknown. One controlled trial of multinutrient supplementation with nutrients related to the Mediterranean diet (including Ω-3 polyunsaturated fatty acids, selenium, folic acid and vitamin D_3) suggested no benefit with regard to the development of an episode of MDD in patients who had depressive symptoms or who had overweight or obesity[106].

The lack of adherence to medical treatment and advice could also underlie the association between

depression and medical disorders and could partly explain why patients with concurrent chronic illness and depression have poorer prognosis than patients without depression[9]. A relationship between depression and poor adherence to medication was reported >20 years ago and has been corroborated in many subsequent investigations. For example, MDD and depressed mood has been associated with reduced adherence to adjuvant endocrine therapy in breast cancer[107] and reduced adherence to self-care advice in heart failure and diabetes mellitus[108,109]. Poor adherence can be divided into intentional non-adherence and unintentional non-adherence; depression seems to be more relevant to intentional non-adherence, although few studies have explored this distinction. Most studies have used self-report measures of adherence, and the results may have been confounded if depression modified reporting behaviour rather than objective adherence. However, studies using measures such as electronic time-stamped pill boxes confirm the self-report findings. For instance, one study in people with acute coronary syndrome showed that adherence to aspirin was negatively related to severity of depressive symptoms[110]. However, this study was not powered to address the association between adherence and cardiovascular adverse events.

Taken together, evidence indicates that behavioural pathways are plausible mediators of the relationship between depression and physical comorbidities and that behaviours may have both protective and adverse effects. However, there are two caveats to this conclusion. First, reductions in smoking, physical inactivity or other risk behaviours have not been demonstrated to break the link between depression and comorbid illnesses. Such studies are difficult to conduct as individuals cannot be randomly assigned to behaviours and as effects would take several years to emerge. Of course, many healthy changes in lifestyle affect comorbid conditions, but these effects may be independent of depression. Second, the majority of prospective observational studies of depression and physical health outcomes have included lifestyle factors such as smoking and physical exercise as covariates, and these studies have frequently found independent associations between depression and comorbidities, even when behavioural factors were accounted for, suggesting that behavioural processes are, therefore, only part of the story.

Psychological factors

The cognitive model views the aetiology of depression within a diathesis–stress model, and can also be used to describe comorbid depression in medical disorders, but requires adaptation in this scenario. For example, medical conditions pose many unique threats or stressors (where a stressor is defined as an event that causes strain or potential harm). If depression is viewed from the standpoint of the stress and coping model, depression in physical illness may occur when the demands of the situation exceed the coping resources of the person[111].

Stressors in physical illness may be both acute and chronic; acute stressors include receiving an initial diagnosis, waiting for test results, waiting for or undergoing medical procedures, and illness flare or progression, whereas chronic stressors include managing an uncertain future, threat of mortality, ongoing self-management and medical management of the illness, dealing with symptoms and disability, appearance changes, and loss of independence[112,113]. Thus, depression in those with a physical disease could be an understandable rather than a pathological reaction to the challenges of living with the condition.

A key adaptive task for the individual is to return to a state of emotional equilibrium after acute illness events and to manage the ongoing load of chronic stressors. The inability to do these tasks may lead to depression through a range of cognitive, behavioural and social factors (FIG. 4), some of which are illness-specific. Other factors such as lack of social support and isolation are important risk factors for depression across medical conditions[114,115]. Intrapersonal factors, such as perfectionism[116] and pessimism[117], may influence attention to somatic states, the interpretation of these states and coping behaviours[118], which in turn may lead to depression. In line with this hypothesis, a longitudinal study in patients with cancer found that perfectionism was associated with more severe depression through hyper-arousability and maladaptive coping strategies, such as emotional preoccupation, resting when tired and avoidance or distraction[119].

The common-sense model (CSM) of illness suggests that these background factors can help shape patients' idiosyncratic perceptions of their illness[120], which can influence behavioural and emotional responses to the illness. Indeed, one review of >300 studies based on the CSM showed that negative illness perceptions, such as viewing the illness as chronic, cyclical or uncontrollable, or as having serious consequences or multiple symptoms, are associated with depression across several medical conditions[121]. Importantly, even after controlling for illness severity, negative illness perceptions explain some of the variance in severity of depression[122]. In addition, growing evidence suggests that everyday interpretations of symptoms, such as catastrophizing (believing in worst-case scenarios) about symptoms or viewing symptoms as signs of biological damage are also key correlates of depression in physical illness[123,124].

Coping behaviours can mediate the effects of illness perceptions on outcome. For instance, strong beliefs in the negative consequences of the illness have a negative effect on depression through avoidance behaviours[121]. The direct role of coping on adjustment outcomes such as depression is sometimes contradictory. This may be, in part, because the adaptiveness of coping behaviours is context-dependent. For example, distraction and denial may be helpful when waiting for test results, but denial of the severity of an illness that requires the taking of medication could be detrimental if it leads to poor treatment adherence. Coping behaviours, such as avoidance and poor self-management, seem unhelpful in most contexts, as they are consistently related to depression[125].

It is also important to consider factors that may protect from depression in the context of physical illness, such as self-compassion (kindness and acceptance towards oneself in the face of suffering)[126]. Self-compassion can foster adaptive coping and,

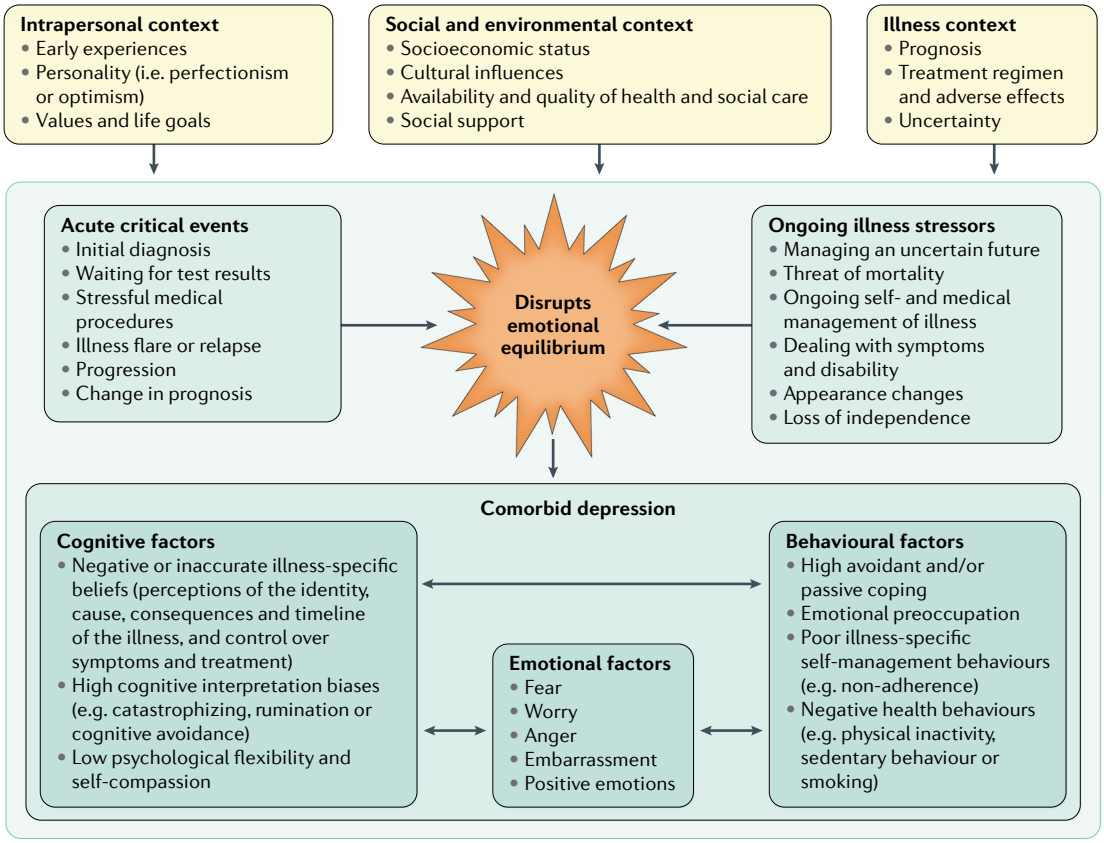

Fig. 4 | **Psychological factors involved in adjusting to chronic illness.** Intrapersonal, social, environmental and illness-related factors can contribute to depression directly and indirectly through cognitive, behavioural and emotional responses to the illness. Adapted with permission from REF.[113], Wiley.

therefore, resilience to illness-related stressors. Indeed, self-compassion was associated with health-promoting behaviours in one meta-analysis[116], and some evidence suggests an association between self-compassion and lower levels of depression among populations with chronic illness, particularly cancer[127–129]. Similarly, psychological flexibility (the capacity to adapt to situational demands and shift perspectives) may protect from depression. In accordance with this, flexibility was lower in patients with depression than in those without depression and inflexibility was associated with greater depression severity in one meta-analysis of 147 studies[130]. This association has been studied less in depression specific to medical conditions, but one study of patients with chronic pain demonstrated that low levels of psychological flexibility predict depression even when adjusting for pain severity[131].

Diagnosis, screening and prevention

MDD is diagnosed according to current diagnostic criteria (according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (BOX 2) or International Classification of Diseases and Related Health Problems, 10th revision (ICD-10)) but diagnosing comorbid depression in patients with medical conditions can be challenging as both mental and physical health disorders can cause similar somatic symptoms. DSM-5 criteria state that symptoms clearly attributable to another medical condition should not be counted towards the five criteria required for a diagnosis of MDD; thus, in patients with fatigue, reduced appetite, diminished interest in activities, psychomotor retardation and changes in sleep, it can be difficult to make a diagnosis of depression. Of note, medical conditions typically do not cause depressed mood, feelings of worthlessness or suicidal ideation, so a predominance of these symptoms makes a medical aetiology less likely. These diagnostic challenges may be further complicated by the possibility that depressive symptoms can also occur as part of another psychiatric disorder (such as bipolar disorder) or the alternative option to code these symptoms as a depressive disorder due to another medical condition using DSM-5 criteria or organic depressive disorder using ICD-10 criteria (see BOX 3). In these cases, it may be helpful to recommend behavioural activation (encouraging patients to increase the frequency of relaxing and pleasant activities) that does not harm medical patients and can improve depression[132].

A normal grief reaction can also result in depressive symptoms, but, even if initially sparked by a significant loss, patients with depressive symptoms lasting >2 months may meet the criteria for MDD[133]. Problem drinking and drug use are also important considerations. However, the presence of substance abuse should not preclude a concurrent diagnosis of MDD. Finally,

Box 2 | **Diagnostic criteria for MDD**

Diagnosis of major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria requires a person experiencing five or more of nine specific symptoms (listed below) most of the time during the same 2-week period, with at least depressed mood or loss of interest or pleasure (anhedonia) being present[287]. In addition, these symptoms must have caused clinically significant distress or impairment in social, occupational or other important areas of functioning and not be attributable to the physiological effects of a substance or to another medical condition. The occurrence of a major depressive episode must not be better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder or another psychotic disorder. Likewise, a history of manic or hypomanic symptoms (which would indicate bipolar disorder) must be ruled out.

1. Depressed mood (feeling sad or empty)
2. Markedly diminished interest or pleasure in almost all activities
3. Increased or decreased appetite; unintentional weight loss or gain
4. Diminished ability to think or concentrate
5. Fatigue or loss of energy
6. Feelings of worthlessness or excessive guilt
7. Agitation or retardation
8. Insomnia or hypersomnia
9. Suicidal ideation

Adapted from REF.[287].

checking a patient's haemoglobin, white blood cell count and thyroid stimulating hormone may be necessary to rule out anaemia, infection and hypothyroidism before initiating therapy for MDD.

Screening

Two 'yes'/'no' questions can be used to screen for MDD (FIG. 5); a 'no' response to both questions effectively rules out depression (that is, there are few false negatives), and no further screening is necessary[134,135]. The WHO, UK and Australian national guidelines recommend use of these two questions for depression screening[136–138]; however, the use of these questions has not yet been validated in all settings, such as in low-income and middle-income countries (LMICs).

These two questions are occasionally confused with the PHQ-2 multiple-choice screening tool, which has weaker test characteristics[139–141]. A score of ≥1 (out of 2 possible points) on the two 'yes'/'no' questions has a sensitivity of 95% and a specificity of 65% for detection of MDD[135], whereas a score of ≥2 (out of 6 possible points) on the PHQ-2 has a sensitivity of 91% and a specificity of 67% for detection of MDD[142]. As both tools have low specificity (leading to many false positives), a positive screen must be followed by a clinical interview to determine whether the patient meets criteria for MDD[141].

As an alternative to a clinical interview, some providers use the nine-item PHQ-9 for both depression screening and diagnosis[143]. The PHQ-9 is a self-report instrument that measures the frequency of each of the nine DSM-IV depressive symptoms experienced over the past 2 weeks, with a total score of up to 27 based on number and frequency of depressive symptoms. The pooled sensitivity for a threshold of at least 10 on the PHQ-9 is 80%, with a pooled specificity of 92%[144]. Other providers use a PHQ-9 algorithm, comprising the PHQ-2 followed by the PHQ-9 for patients who screen positive. Using a threshold of ≥2 on the PHQ-2 and ≥10 on the PHQ-9, the PHQ-9 algorithm has a sensitivity of 58% and a specificity of 92%[145]; however, the area under the receiver operating characteristic curve was significantly lower for the PHQ-9 algorithm (0.73) than for either the PHQ-2 (0.86) or PHQ-9 (0.91) alone in one meta-analysis[145].

Making a diagnosis of MDD based on a PHQ-8 or PHQ-9 score of ≥10 if one of the two core features of MDD (depressed mood or anhedonia) is present, and the symptoms are associated with functional impairment, is reasonable. However, in some patients, a threshold of ≥10 on the PHQ-9 misses MDD that could be detected by the clinical interview. The advantage of using the two 'yes'/'no' questions is that they are highly sensitive, take <1 minute to complete and rule out MDD in more than half of patients[135]. By contrast, the PHQ-9 can serve as both a screening instrument and a diagnostic tool, thereby eliminating the need to further evaluate false-positive screens.

The optimal frequency of depression screening has not been determined. In the absence of data, a pragmatic approach is to screen all adults with a medical disorder who have not been screened previously and use clinical judgement, considering risk factors, comorbid conditions and life events, to determine whether additional screening of patients at high risk of depression (such as pregnant and post-partum women) is warranted.

Of note, screening or case-finding for MDD does not improve clinical outcomes unless it occurs within the context of a collaborative care team with a trained care manager and a consulting psychiatrist[146,147]. The care manager provides patient education, behavioural activation, monitoring of symptoms and adherence to therapy, timely follow-up and individualized treatment augmentation for non-responders. The consulting psychiatrist helps the care manager by supervising and assisting with patient management and medication adjustment. However, a collaborative care team depends on the availability of resources and may not be feasible in all settings, such as LMICs.

As most specialty practices cannot provide the collaborative care management that is necessary for depression screening to benefit patients, screening is best conducted in the primary care or general practice setting. As some specialty providers, such as oncology and dialysis centres, tend to function as primary care providers, depression screening may be of benefit, assuming a trained depression care manager and consulting psychiatrist are in place. However, for the most part, medical and surgical subspecialists should not be expected to provide screening or treatment for depression.

Management

The general guidelines for the treatment of depression[1] also apply to comorbid depression in patients with medical disorders. Depending on the severity and course of both the medical condition and depressive symptoms as well as informed patient preferences, the main treatment strategies include psychotherapy, pharmacotherapy (BOX 4), self-management and treatment of

the underlying medical disease, ideally provided in an integrative care setting including several care providers and subspecialties (FIG. 6). Additionally, we discuss the comorbidity of MDD and pain, which is a symptom rather than a disease entity, separately in BOX 5. Issues such as treatment-resistant depression or psychotic depression and treatment approaches to these severe conditions are beyond the scope of this Primer and are discussed in greater detail in the Primer on MDD[1].

Pharmacotherapy

Deciding which antidepressant drug to administer to a patient with comorbid depression is affected by the medical disorders and their treatment, together with other factors such as the patient's age, presence of pain, polypharmacy, severity and course of the current depressive episode, and previous antidepressant trials.

Efficacy. Antidepressants in patients with MDD have low to moderate effect sizes (with standardized mean differences (SMDs) of 0.17–0.49)[148]. Interestingly, larger effects of antidepressants, compared with placebo, have been found for comorbid depression in some medical diseases showing a SMD of 0.66 and a number needed to treat of 6 (REF.[149]), particularly for coronary heart disease[150], cancer[151], type 2 diabetes mellitus[152] and neurological disorders[153], including post-stroke depression[154], Parkinson disease[155] and MS[156] (TABLE 1). Whether these differences in response are due to smaller placebo responses, synergistic drug effects or other common biological pathways in those with a medical disorder is unknown. However, other meta-analyses have found lower effect sizes of antidepressants in those with cancer[157] and rheumatoid arthritis[158], and insufficient evidence in IBD[159] (TABLE 1). Furthermore, studies used different definitions for comorbid depression and several meta-analyses were based on a few low-quality RCTs, potentially inflating the effect size. Thus, although some evidence indicates good efficacy of antidepressants in those with comorbid depression, few sufficiently powered RCTs have been performed.

Safety. Drug–drug interactions and adverse effects complicate the treatment of comorbid depression. Drug–drug interactions can be caused by pharmacodynamic interactions (that is, one drug directly affecting the other drug), which is more common with older antidepressants, or pharmacokinetic interactions by interfering with renal excretion or hepatic metabolism. Hepatic cytochrome P450 (CYP) is an isoenzyme superfamily, with six members (including CYP2D6 and CYP3A4), that is involved in metabolizing >90% of all drugs[160]. Pharmacogenomic testing can identify rapid or slow metabolizers and preliminary evidence suggests that testing can improve response and remission rates in depression[161]. Helpful free mobile apps for checking drug–drug interactions include MedScape, GenieMD and CVS Caremark, and studies have systematically reviewed apps for consumers[162] and health professionals[163].

The use of antidepressants in people with comorbid depression has been associated with lower tolerability owing to a greater number of adverse effects in comparison with placebo in some[153,154] but not all[157] meta-analyses. However, several clinical trials have not provided sufficient data regarding tolerability, therefore, this important clinical aspect could not be addressed in other meta-analyses[150,152,164].

For specific adverse effects, a cardiotoxic profile is established for tricyclic antidepressants (TCAs)[165] and monoamine oxidase inhibitors[166]; thus, these drug classes should be avoided in patients with heart disease. By contrast, selective serotonin reuptake inhibitors (SSRIs), particularly sertraline, seem to be safe in terms of cardiotoxicity[167] and their use has been recommended in these patients (TABLE 1). Prolongation of the QTc interval may lead to arrhythmias, and a meta-analysis demonstrated that QTc prolongation was more common in patients taking TCAs than in patients taking SSRIs[168]. However, some SSRIs (escitalopram and citalopram) are also associated with QTc prolongation[168,169] and should be used with caution. Several drugs used for medical conditions can also affect the QTc interval, such as some antibiotics, and antihistamine and antiarrhythmic agents, further increasing the risk. Accordingly, combining antidepressants that cause QTc prolongation with other drugs that prolong the QTc interval should be avoided and consultation of drug–drug interaction databases is highly recommended (see Related links). In circumstances in which co-prescription of these drugs is necessary, strict monitoring of the QTc interval is warranted.

Furthermore, some SSRIs may lead to higher plasma levels of calcium antagonists and β-blockers; thus, these drugs require dosage adjustment in patients taking SSRIs[170]. By contrast, combining SSRIs with statins and renin–angiotensin system drugs seems safe and may even improve depression outcomes[171]. Putative

Box 3 | **Diagnostic challenges and psychiatric comorbidities**

Diagnosing comorbid depression in people with medical diseases can be challenging for several reasons. First, as is the case for the diagnosis of major depressive disorder (MDD) in general, depressive symptoms can appear in the context of other affective disorders such as dysthymia or bipolar disorder. Second, depression is often comorbid with other psychiatric disorders, particularly anxiety disorders, such that a comprehensive diagnostic workup is required. For example, from a clinical point of view, it is important to differentiate between MDD with anxious distress as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) that is likely to resolve with improved depression and a genuine anxiety disorder that might persist even after successful antidepressive treatment.

Moreover, diagnostic criteria (such as in DSM-5 and/or the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10)) allow the coding of depressive disorders secondary to medical disorders. In the DSM-5, this is specified as a Depressive Disorder due to Another Medical Disorder, whereas the ICD-10 refers to it as Organic mood (Affective) disorder. In practice, this poses the diagnostic dilemma to make a judgement whether the medical and the mood disorder are causally related or simply co-occur. This relationship is likely to be complex with many factors contributing, so that inferring a clear causality (as would be suggested by the diagnosis of Depressive Disorder due to Another Medical Disorder or Organic mood (Affective) disorder) can be challenging. An organic cause seems highly plausible in some patients (such as an acute infection), particularly if there is a close temporal correlation with onset of the depressive disorder and/or if depressive symptoms subside after appropriate treatment of the medical disorder. However, in most patients, this will remain uncertain, and the pragmatic approach is typically to code both the medical disease and the depressive disorder separately.

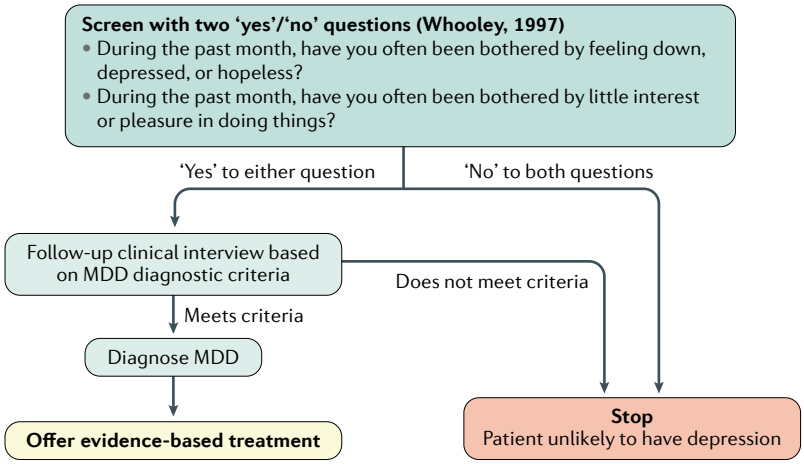

Fig. 5 | **Algorithm for diagnosing depression in patients with comorbid medical diseases.** A two-question instrument can be used to identify patients at risk of clinically relevant depressive symptoms. A positive result (that is, answering 'yes' to one or both questions) warrants an in-depth psychiatric evaluation. MDD, major depressive disorder. Image courtesy of M. A. Whooley.

antidepressive effects of statins may be due to their effects on the immune system[172] or direct effects in the CNS, in which they have been shown to affect neuroplasticity, neurotransmission and excitotoxicity, although data are from animal studies only. Some antidepressants, particularly SSRIs, can also increase the risk of bleeding by inhibiting serotonin in the coagulation cascade[173]. NSAIDs and acetylsalicylic acid further increase this risk, which is reduced by proton pump inhibitors[173]. In addition, anticoagulant therapy with warfarin may interact with some antidepressants, leading to higher plasma levels of warfarin, necessitating closer international normalized ratio monitoring (INR; which assesses blot clotting)[174].

Antidepressants have been associated with an increased risk for type 2 diabetes mellitus[175], and some antidepressants (particularly TCAs and mirtazapine) may lead to weight gain[176]. These adverse effects do not preclude the use of these therapies, although close monitoring of BMI and plasma glucose and lipid levels is required after initiation. SSRIs seem to have a better benefit–risk ratio than other classes of antidepressants and are recommended as first choice in patients with diabetes mellitus[151,152,177]. Bone resorption may be affected directly by SSRI and medical drugs and indirectly by depression and medical diseases[178,179], increasing the risk of osteoporosis and fractures. Thus, bone density should be assessed during long-term treatment in patients at high risk of osteoporosis. Some antidepressants, particularly SSRIs and bupropion, may lower the seizure threshold, but the risk is low in people with well-controlled epilepsy[180]. In addition, some anticonvulsants, such as carbamazepine, can reduce TCA plasma concentrations, whereas valproic acid can increase plasma levels[181], potentially necessitating dosage adjustments. Combination of sedating antidepressants such as TCAs or mirtazapine with CNS-depressant drugs, such as benzodiazepines or some antihistamines, may result in sedation and lower cognitive functioning[182].

Effect of treatment of underlying medical diseases on depression. As previously discussed (Mechanisms/pathophysiology, above), some treatments may actually exacerbate or even cause development of depressive symptoms; however, successfully treating the underlying medical disorder may also reduce depressive symptoms, either directly (by targeting biological pathways that are shared between the medical disorder and depression, such as inflammation) or indirectly by reducing pain and other symptoms of the medical disorder. One notable example of this point that needs to be replicated in further studies is the antidepressive effect of biologicals targeting IL-6 and IL-12/IL-23 in inflammatory disorders, which is evident even in patients who do not respond in terms of their physical symptoms (see REFS[72,73]). However, anti-inflammatory treatments or immune-modulating treatments are not part of the standard care for MDD even in patients with inflammatory disease. In patients with MS, one meta-analysis did not find any evidence that disease-modifying therapies induce depression but some therapies (for example, fingolimod) may reduce depressive symptoms[183]. Interestingly, treatment guidelines for patients with Parkinson disease and comorbid depression first recommend a sufficient dopaminergic treatment, with additional treatment with antidepressants only in those with no improvement in depression[184].

Psychotherapy

Psychotherapeutic approaches in patients with medical disorders differ from those in patients without a medical illness in several ways. Given the multifaceted causes of comorbid depressive symptomatology, the goals and setting of psychotherapeutic interventions in patients with a medical illness and comorbid depression need to be carefully planned. The time frame for psychotherapeutic interventions is often limited and patients can only be seen a few times owing to, for example, time-consuming invasive treatments, progressive disease and/or a decreasing physical and/or mental health status (for example, limited cognitive capacity). This limited time frame may have implications for the development of a trustful and sustainable therapeutic relationship and psychotherapeutic treatment planning. Psychotherapeutic treatment planning often depends on the course of the disease and changing supportive care needs of patients. Psychotherapy for people with medical illness requires broad knowledge of common treatments and treatment adverse effects and a close collaboration and communication with the professional health-care team.

Psychotherapeutic interventions in patients with cancer or other severe medical disorders can usually be characterized as supportive therapy that aims to help patients deal with distressing emotions by reinforcing pre-existing strengths, social support, and promoting adaptive coping with the disease[185]. Frequently used therapeutic techniques and multimodal approaches are derived from both cognitive and behavioural techniques and/or psychodynamic treatment approaches and include information, psychoeducation and counselling, emotion regulation and relaxation, learning and

problem-solving, crisis intervention, mindfulness-based and meaning-focused interventions as well as supportive presence. Types of psychotherapeutic intervention include those delivered to individual patients, to couples and to groups[185].

Individual and group intervention RCTs in patients with cancer who were preselected according to increased distress but not necessarily with depression have shown a medium effect size (*d*) of 0.53 (95% CI 0.27–0.80) in post-treatment depression[186]; psychotherapeutic interventions included in this analysis comprised coping skills training, cognitive behavioural therapy (CBT), supportive–expressive psychotherapy, relaxation and imagery techniques and psychoeducation on health education and stress management. In patients with advanced, incurable cancer, psychotherapeutic interventions are associated with moderate decreases in depression scores, typically measured by validated and established screening measures such as the PHQ-9 compared with control conditions with a SMD of 0.67 (95% CI 0.29–1.06)[187]. Longer durations of psychotherapy are associated with larger effects on depression, but only beyond a 6-month follow-up interval, suggesting that sustained effects require longer treatments[186]. Most RCTs have been performed in patients with breast cancer, which could be due to the high prevalence of breast cancer, the high depression rates in these patients or a propensity of patients with breast cancer to participate in psychological treatment trials. By contrast, RCTs of the effect of psychotherapeutic interventions on depression in patients with other types of cancer are relatively scarce[186,188,189]. Few studies have focused on patients with clinically diagnosed depression, with most studies relying on subjective outcomes measured with self-administered questionnaires[187]. The most established screening measures for depression in patients with a medical illness including the Hospital Anxiety and Depression Scale (HADS) and PHQ-9 may have insufficient diagnostic accuracy in patients with cancer[190], leading to a large number of false-positive cases when sufficiently sensitive cut-off scores are used. Thus, there might have been a risk of overestimating clinical depression in these trials.

Similarly, psychotherapeutic interventions have been shown to have some beneficial effects on MDD or depressive symptoms in patients with other medical disorders. For example, CBT seems to be effective for the treatment of post-stroke depression with a SMD of −0.83 (95% CI −1.05–0.60), according to one meta-analysis of 23 studies[191]. However, an earlier Cochrane meta-analysis[192] did not find beneficial effects of psychotherapy in people with post-stroke depression, which may have been related to the lower number of studies included in the analysis or the more rigid methodology. Meta-analyses have also shown benefits of CBT and mindfulness-based treatments for depression in patients with Parkinson disease[193] or MS[193,194] but no RCTs in Huntington disease have been published. Meta-analyses have also shown that CBT can significantly reduce depression in patients with cardiovascular disease (SMD −0.35, 95% CI −0.52 to −0.17)[195] and diabetes mellitus (SMD −0.65, 95% CI −0.98 to −0.31)[196]. The latter finding contrasts with that of one Cochrane meta-analysis[197] of the effects of psychological interventions on diabetes mellitus-related distress showing that none of the evaluated psychological interventions improved diabetes mellitus-related distress more than usual care. These conflicting conclusions are likely to be due to the authors' assessment of the study quality of trials in this area. Emerging evidence suggests that third-wave therapies such as acceptance and commitment therapy may reduce depression in patients with medical disorders such as cancer and epilepsy[198].

It should be noted that the quality of RCTs of psychological interventions is often low, and clear evidence for the efficacy or effectiveness of these interventions is lacking for most, if not all, disease areas. Methodological weaknesses include risk of bias, lack of information about indicators of study quality (such as randomization procedures), lack of allocation concealment and

Box 4 | **'Do's and 'don't's of pharmacotherapy for comorbid depression**

Do

- Include patient and relatives in decision-making
- Discuss treatment plan with physician treating the patient's medical condition
- Thoroughly explain the onset of action of antidepressants to both the patient and the patient's other physician
- Carefully take the patient's history and signs and symptoms to determine whether there is an increased risk of a specific adverse event
- Consider the patient's age and medical comorbidity prior to medication and be especially cautious in older patients in whom medication should be started with a low dose that should then be titrated slowly ('start low, go slow')
- If you plan to add any new medication to any existing medication, double-check if there are potential drug interactions (see Related links)
- Determine weight and baseline laboratory values before treatment with medication (at least electrolytes, liver enzymes, creatinine, fasting glucose, lipids and haemogram)
- Conduct electrocardiography (ECG) prior to treatment with antidepressant medication and determine baseline QTc time
- Monitor laboratory values, weight and ECG in the course of pharmacological treatment at least every 6 months
- Check whether the indication for each medication is still present or whether any drug can be tapered down or off at least once a year

Don't

- Do not ignore the medical condition. Assess whether the medical underlying cause of depression should first be treated, whether the symptoms are indicative of a depressive episode or something else, such as hypoactive delirium, and whether the medication recommended is contraindicated in this specific medical condition
- Do not ignore the psychosocial situation of the patient; that is, initiate psychotherapy, financial counselling, among others, if necessary
- Try to avoid polypharmacy in older people whenever possible[a]
- Try to avoid benzodiazepines, tricyclic antidepressants and antipsychotics in older people
- Do not use antipsychotics routinely as a sleeping aid
- Do not ignore weight gain in the course of pharmacological treatment
- Do not underestimate the impact of depression on quality of life and the course of comorbid medical illness; that is, treat depression 'aggressively'

[a]Inappropriate polypharmacy is present when one or more drugs are prescribed that are not or no longer needed because there is no evidence-based indication; the indication has expired or the dose is unnecessarily high; one or more medicines are failing to achieve the therapeutic objectives they are intended to achieve; or one drug, or the combination of several drugs, are causing unacceptable adverse drug reactions, or put the patient at an unacceptably high risk of such reactions. Adapted from REF.[288].

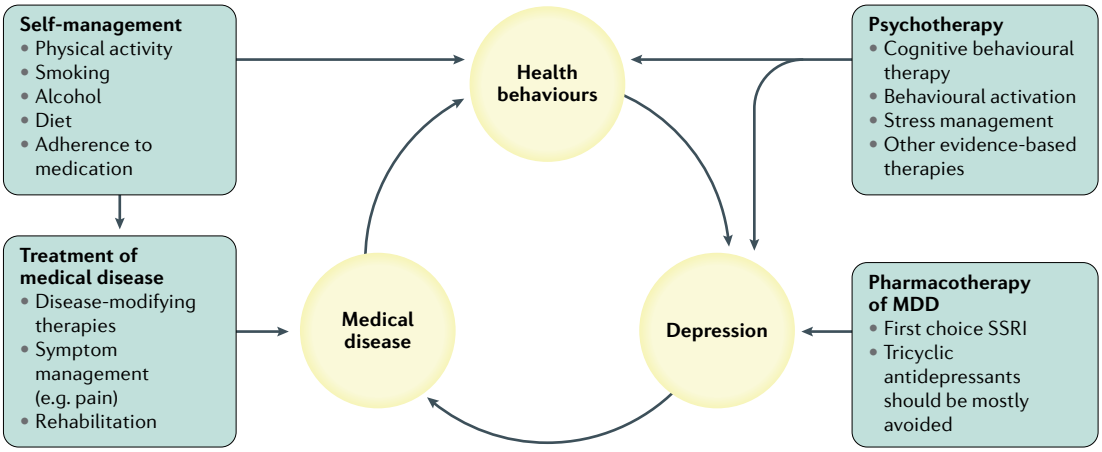

Fig. 6 | **Interdisciplinary care for comorbid depression.** Treatment of depression in people with medical diseases consists of four pillars (self-management, psychotherapy, treatment of the medical disease and pharmacotherapy of major depressive disorder (MDD)) that ideally should be combined in interdisciplinary, comprehensive care. In terms of psychotherapy, cognitive behavioural therapy has the most supporting evidence. The potential benefits and harm of the medication need to be weighed carefully for pharmacotherapy of both MDD and the medical disease (see BOX 4). Additional important aspects include the thorough treatment of the comorbid medical disease and modification of behaviours that might additionally elicit antidepressive effects or reduce risk factors such as smoking cessation, increasing physical activity and improving diet. SSRI, serotonin reuptake inhibitor.

blinding, and selective outcome reporting probably associated with exaggerated effect estimates[186]. Another frequent problem is incomplete follow-up data probably caused by poor prognosis or deterioration of the health of patients with progressing or advanced disease[186,187]. A problem with psychotherapy trials in general relates to the choice of control groups, where many trials have used waitlist control groups and other non-active comparators[199], and this is also a problem with trials in patients with comorbid depression and is likely to have led to treatment effects being overestimated.

Neurostimulation

Electroconvulsive therapy (ECT) should be considered in addition to other treatment modalities in patients with severe treatment-resistant depression, those with psychotic depression or those with depression and acute suicidality[200,201]. Importantly, older age and more severe depression are robust predictors for responding to ECT[202]. The potential benefits and adverse effects of ECT treatment should be assessed carefully in patients with MDD and comorbid medical diseases. The most common adverse effect of ECT is impaired cognitive function; however, one meta-analysis demonstrated that these objectively measured effects are restricted to the first three days after treatment, with an improvement in several cognitive variables such as processing speed, working memory, anterograde memory and executive function beyond baseline levels two weeks after treatment[203]. However, ECT should be reserved for patients with the most severe MDD and/or after several other treatments have failed. Other neuromodulatory treatments such as transcranial magnetic stimulation (repetitive transcranial magnetic stimulation or transcranial direct current stimulation) have shown promising results in terms of efficacy and safety in one network meta-analysis[204] and might be additional options in the treatment of patients with MDD and comorbid medical diseases.

Barriers to treatment

Although evidence supports the efficacy of both pharmacological and psychotherapeutic interventions for depression in people with medical disorders, in some cases, it can be difficult to deliver treatments to these patient groups. This issue applies in both LMICs and high-income countries. Barriers to treatment for comorbid depression can include symptoms (such as mobility problems, fatigue or cognitive impairment associated with the medical disorder), treatment of the medical disorder (such as hospitalizations) and resources in health-care systems. For example, LMICs face major challenges in health-care delivery and, in general, health-care systems in LMICs are structured to respond to acute conditions.

Multimorbidity, the coexistence of multiple chronic conditions[205], and the chronicity of care require a different engagement with people beyond one-off interactions[206]. In this context, the application of digital health technologies (via mHealth or eHealth tools), integration of care and task shifting has been highly innovative in LMIC settings, including the use of digital mental health resources and pragmatic mHealth-delivered treatment[207–210] for the management of depression among people with existing physical comorbidities. Indeed, moving away from addressing single diseases towards the integration of care seems to be a suitable response in LMICs[211–213].

The field of digital health or mHealth has received much attention over the past few years[214,215]. In terms of health systems, digital tools are directly linked to several aspects, including education, data generation, several health care-related processes and clinical management[214]. One of the advantages of mHealth,

particularly in the field of mental health, is the possibility of establishing contact and engagement beyond a physical infrastructure[216–218]. Another clear use of mHealth has been in maximizing the linkage to existing mental health care, without the need for additional resources or providing new services[219,220]. Other ongoing initiatives are using mHealth technologies to deliver short-term problem-solving intervention strategies for treatment of mild to moderate depressive symptoms among patients with cardiometabolic conditions[207–209], and some web-based strategies seem to be cost-effective[221–223], although long-term evaluations are needed. Another important innovation in depression treatment in LMICs has been the provision of problem-solving therapy by lay health-care workers in Zimbabwe showing reduction of depression symptoms at 6 months in primary health clinics and facilities[224].

eHealth options have also been explored in other settings. A meta-analysis of internet-delivered CBT (iCBT) for several medical disorders including rheumatoid arthritis, cardiovascular disease, diabetes mellitus and cancer demonstrated significant but small effects in ameliorating depressive symptoms[225]. Furthermore, individual trials have suggested the efficacy of iCBT for the treatment of depression in patients with MS[226] and epilepsy[227], with small to moderate effects compared with waitlist control groups.

Comprehensive care

Other treatment approaches beyond pharmacotherapy and psychotherapy often have an important role in the treatment of depression in medical diseases. Moreover, the care of these patients requires close cooperation between all health-care professionals from all disciplines involved, and it is reasonable to assume that patients with comorbid depression and medical diseases benefit from interdisciplinary, coordinated care. This care should include strategies to improve self-management and lifestyle, and measures to manage the risk of severe depression symptoms including suicidal thoughts and suicidality.

Self-management. Self-management strategies can include lifestyle modifications such as quitting smoking or changing dietary habits. In particular, physical exercise has emerged as a very promising approach to the treatment of depression in patients with chronic diseases. Indeed, one meta-analysis of 90 studies with >10,000 participants[228] found that exercise reduced depressive symptoms among patients with a chronic illness with a small-to-moderate effect size (*g*) of 0.30. These findings have been corroborated in several large high-quality trials in patients with medical diseases, including coronary artery disease and chronic heart failure[229,230]. Exercise programmes have also been shown to have small-to-moderate effects in reducing depressive symptoms in patients with neurological disorders, including MS[231], inflammatory disorders and rheumatoid arthritis[232]. Of note, methodological limitations such as unblinded interventions (Psychotherapy, above) need to be taken into account when appraising the findings and their effect sizes.

Suicide prevention. Many studies have found increased suicides rates in patients with chronic medical disease; for example, one historical cohort study of >6,000,000 Swedes demonstrated a relative risk of suicide among patients diagnosed with cancer of 12.6 during the first week and 3.1 during the first year, compared with people without cancer[233]. This increased risk of suicide in patients with cancer has been confirmed in several other large-scale studies[234,235].

An increased risk of suicide has also been found in other patient populations. For example, suicide rates are also increased in patients with type 1 and 2 diabetes mellitus, as confirmed by a meta-analysis[236] and a systematic review[237]. In addition, one nationwide study in Denmark demonstrated significant excess adjusted incidence rate ratios of 4.9 (95% CI 3.5–6.9) for amyotrophic lateral sclerosis, 4.9 (95% CI 3.1–7.7) for Huntington disease, 2.2 (95% CI 1.9–2.6) for MS, 1.7 (95% CI 1.6–1.7) for head injury, 1.3 (95% CI 1.2–1.3) for stroke, and 1.7 (95% CI 1.6–1.8) for epilepsy[238]. Importantly, the last clinical contact for the majority of people who die by suicide is either in an emergency department or in primary care settings[239], underscoring the need to be aware of potential suicidal thoughts and ideations in medical care.

Collaborative care. Collaborative care refers to a multiprofessional treatment approach in which a physician and at least one other health professional deliver care to patients within a structured management and intervention plan that includes regular follow-up visits and an emphasis on inter-professional communications within the team[240] (FIG. 6). Indeed, several meta-analyses of studies in different diseases have established the efficacy of collaborative care in patients with comorbid depression. For example, collaborative care interventions were more effective than usual care in patients with cancer, with an SMD of 0.49 (REF.[241]). In patients with type 2 diabetes mellitus and depression, collaborative care

Box 5 | **Depression and pain**

Pain is a very common symptom in many medical diseases across all disciplines, including cancer[289], rheumatoid arthritis[123], inflammatory bowel disease[290], type 2 diabetes mellitus[291] and Parkinson disease[292]. Indeed, one meta-analysis found that 39% of patients with cancer reported pain after curative treatment, 55% of patients reported pain during anticancer treatment and 66% of patients with advanced, metastatic or terminal disease reported pain. Importantly, moderate to severe pain was reported by 38% of all patients[289].

Unsurprisingly, pain is a very strong predictor of depression and vice versa. Among many other examples, the presence of pain is associated with a 2.5–10-fold increased risk of comorbid depression[293] in primary care cross-sectionally, with a 2–4-fold increased risk of newly developing depression over 4 years[294]. Importantly, one meta-analysis of studies from low-income and middle-income countries confirmed very high comorbidity rates, finding a prevalence of 34% for severe pain in patients with major depressive disorder[295]. Furthermore, pain is a strong predictor for non-remission during antidepressive treatment[296] and for recurrence of depressive episodes (as opposed to the medical illness itself[297]).

Thus, the successful treatment of pain is essential to successfully treat depression (and vice versa). In other words, antidepressive treatment is pain treatment that, in turn, is antidepressive treatment. As a general rule, serotonin–noradrenaline reuptake inhibitors and cognitive behavioural therapy have been effective in treatment of both pain and depression and are, therefore, recommended in many guidelines[298,299].

Table 1 | **Treatment recommendations for comorbid depression**

Medical disease	Recommended medication	Medications not recommended	Efficacy		Specific safety aspects	Evidence		Refs
			SMD (95% CI)	NNT		No. of RCTs	*n*	
Coronary heart disease	SSRIs (especially sertraline), with mirtazapine as second choice	TCAs	0.71 (0.30–1.11)	3.6	QTc time, bleeding	11	1,685	150
T2DM	SSRIs	TCAs and mirtazapine	0.61 (0.27–0.94)	ND	Weight gain	7	306	152
Neurological diseases (general)	SSRIs	None	0.61 (0.10–1.13)	7	Bleeding, may lower seizure threshold	8	566	153
Stroke	SSRIs, particularly paroxetine	None	0.96 (0.51–1.41)	ND	Bleeding	11	740	154
Multiple sclerosis	None	TCAs	0.63 (0.20–1.07)	ND	None reported	3	165	156
Parkinson disease	None	None	0.54 (0.24–0.83)	ND	None reported	7	257	155
Rheumatoid arthritis	None	None	0.49 (−0.10 to 1.07)	ND	None reported	6	295	158
Cancer (general)	SSRIs and mianserin	TCAs	0.45 (−0.11 to 1.01)	ND	None reported	10	855	157

The presented studies are based on a literature search identifying the most recent meta-analyses for each disease including randomized controlled trials (RCTs) investigating the antidepressant effects of antidepressant drugs in patients fulfilling the criteria for major depressive disorder. ND, not determined; NNT, number needed to treat; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor; T2DM, type 2 diabetes mellitus; TCA, tricyclic antidepressant.

significantly improved depression with an SMD of 0.32 and even improved HbA_{1c} levels (weighted mean difference −0.33%) compared with control conditions[242]. In addition, reductions in depression were evident (standardized mean 0.31) and remission of depression was more likely to be achieved with collaborative care compared with usual care, a waiting list control group or no further treatment in patients with coronary heart disease and depression[243].

Quality of life

Assessing QOL

As one of the first so-called patient-reported outcomes (PROs), health-related QOL (HRQOL) in medicine has been conceptualized as a construct covering physical, social, emotional, cognitive and behavioural components of subjectively perceived health from the patient perspective[244]. Instruments assessing HRQOL across the general population (generic instruments) or within conditions (specific instruments that are targeted to a distinct disease) have been carefully designed, psychometrically tested and translated into multiple languages, to be used as health indicators or outcomes in a wide range of epidemiological, clinical, health economic and quality assurance studies[245]. Established HRQOL generic tools are the SF-36 (REF.[246]), the WHOQOL-BREF[247] and the EQ-5D[248], and of the condition-specific measures, the cancer-specific EORTC-QoL-C30 questionnaire[249].

Despite the distinct features of these instruments, they all assess physical and mental components of perceived health; the assessment of mental components makes the distinction between symptoms of depression and patient-perceived HRQOL mental health quite challenging. Owing to the strong overlap between depression and emotional well-being, both constructs have been viewed as nearly identical, rendering the impact of depression on HRQOL seemingly tautological. Although the mental health component covaries with depressive symptoms, some evidence has shown that the proportion of variance in the mental health component explained by depression is smaller than expected[250]. Furthermore, non-mental HRQOL domains do not differ between people diagnosed with depression and those with other mental or somatic conditions or those without a diagnosis of depression[251].

QOL and chronic medical diseases

A wide range and diverse levels of impairments in HRQOL in terms of patient-reported well-being and functioning have been reported in patients with chronic medical disorders[252]. However, whether poor HRQOL is the direct consequence of a medical diagnosis is debatable, as is the assumed strong association between clinically defined and patient-reported health status[253]. For example, patients reporting better HRQOL after heart transplantation than healthy peers, or patients with cancer with high HRQOL scores even during progressive disease, can be attributed to adaptive processes such as successful coping or re-evaluation of current health in terms of response shift[254,255].

Although much data links chronic medical disorders with depression or with HRQOL, comparatively few studies have addressed the effect of comorbid depression on HRQOL in patients with medical disorders[256,257]. Studies in adults have investigated the burden of disease and depression in terms of HRQOL in those with prevalent conditions such as cancer, diabetes mellitus, heart disease or pain syndromes[258,259]. Patients with both chronic conditions and depression have been reported to have a lower HRQOL than patients with chronic conditions but without depression[4,260]. In these patients, HRQOL is modulated by the consequences of the chronic condition (for example, patient burden, prognosis and treatment options), patient characteristics (such

as psychosocial resources, coping and resilience) and the level of depression (mood impairments, depressive symptoms and diagnosis of depression)[261].

Monitoring HRQOL for clinical research

Monitoring HRQOL may be helpful in screening for comorbid depression in the course of disease and treatment. However, few studies have monitored HRQOL outcomes or have evaluated the benefit of interventions for comorbid depression[262,263]. In these studies, HRQOL outcomes only partially improved after antidepressive interventions[263–266]. Even fewer studies have addressed the interplay between comorbid depression and anxiety[267]. An increased emphasis on including PROs such as HRQOL in clinical trials is reflected in guidelines issued by regulatory bodies such as the European Medicines Agency[268] and the FDA[269]. However, future efforts are needed to assess the effects of non-pharmacological interventions on HRQOL in terms of their cost–benefit ratio[267]. Although the evidence for the benefits of depression monitoring and antidepressive interventions in patients with chronic medical disorders is still limited, there are reasons to expect improvements in disease burden, treatment adherence and prognosis. Patient-reported HRQOL can serve as an indicator of subjective health, as a relevant outcome parameter, and as a mediator or moderator of desired clinical outcomes.

Outlook

Comorbid depression is frequent in people with medical diseases and disorders. The presence of depressive symptoms has profound implications for the psychosocial burden of disease in these patients and poses substantial challenges to the provision of care.

With regard to the treatment of comorbid depression, the most important issue is to better understand what works and what does not in which context. Most studies in patients with medical comorbidities have been comparatively small so that systematic reviews in a given field (such as cancer[157] or MS[270]) are often forced to conclude that the evidence is insufficient to make any specific recommendation. High-quality studies of psychotherapy, lifestyle modifications and other behavioural interventions are also largely lacking, such that evidence-based recommendations are not available for depression in most medical disorders. Consequently, general recommendations are used for the treatment of MDD that do not take into account a patient's comorbidity. The few exceptions to this typically involve recommendations to avoid certain antidepressants owing to known adverse effects that are expected to exacerbate medical disorders. Ultimately, a better evidence base to guide treatment decisions is urgently needed. As the incentives for the pharmaceutical industry to carry out RCTs of already licensed drugs in patients with comorbid medical disorders may be limited, more comparative studies on efficacy and safety of antidepressants in people with medical disorders should be conducted by academic investigators and sponsored by the payers or governmental sources with a strong interest in producing this evidence. Obviously, this is also true for examining behavioural interventions.

To develop new pharmacological strategies that directly target specific biological pathways of comorbid depression in a given medical disorder, more mechanistic insight into this association is needed. This research will be crucial to determine whether depression is 'just' a comorbidity that is essentially identical to MDD without a comorbid medical disorder or whether there is a (biological) interaction between depression and a medical disorder that might require additional or altogether different therapeutic strategies. This line of investigation is likely to benefit from the establishment of convincing animal models, as seen for the comorbidity of obesity and depression.

An additional strategy to learn more about the biological mechanisms might involve ancillary studies in RCTs of disease-modifying therapies in medical disorders that include depression as a secondary outcome. Such studies have already produced some evidence suggesting that depression in inflammatory disorders may — at least in part — be related to immunological mechanisms, and may respond to anti-inflammatory therapies (such as REFS[72,171]). Similar approaches could be used in trials that repurpose drugs in such a setting, such as NSAIDs, minocycline, statins and cyclooxygenase 2 inhibitors.

Different research strategies in comorbid depression, including epidemiological observations, case–control and cohort studies, clinical trials and animal models, each have different strengths and weaknesses and, ultimately, converging evidence from each of these strategies will help elucidate the causal factors involved in the comorbid occurrence of depression and medical disorders. Genetic and Mendelian randomization analyses might be another informative way of dissecting association from causation, as demonstrated for obesity and subtypes of depression[55].

Mental health awareness is increasing in the general public, and effective screening and early treatment of depression is certainly important in people with medical disorders, particularly in primary care. Although screening for MDD in medical settings seems sensible, it is important to point out that different guidelines come to different conclusions regarding the value of systematically screening for depression[271–273]. Even following the diagnosis of comorbid depression, initiation of treatment can be difficult as patients with a comorbid chronic illness may encounter additional barriers to psychiatric care. This issue may best be addressed by establishing comprehensive care models, ideally at the point of entry, that include specialists from the respective medical discipline, psychiatrists or psychologists, and health professionals from other relevant fields. This may also include the integration of novel models of care (such as eHealth and mHealth tools) that could help overcome some barriers, specifically in patients with comorbid medical disorders, at least as adjunct treatments or low barrier options in a stepped care model. However, before this can be carried out, the efficacy, safety and suitability of such tools needs to be clearly established in rigorous clinical trials.

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