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Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is a debilitating disease characterized by depressed mood, diminished interests, impaired cognitive function and vegetative symptoms such as disturbed sleep or appetite. MDD occurs about twice as often in women than in men and affects 1 out of every 6 adults during life.

The etiology of MDD is multifactorial and its heritability is estimated to be around 35%. In addition, environmental factors such as sexual, physical, or emotional abuse during childhood are strongly associated with the risk of developing MDD. There is currently no established mechanism that explains all aspects of the disease. However, MDD is associated with alterations in regional brain volumes, particularly the hippocampus, and with functional changes in brain circuits such as the cognitive control network and the affective-salience network. Furthermore, disturbances in the major neurobiological stress-responsive systems including the hypothalamic-pituitary-adrenal axis and the immune system are present in MDD. Treatment primarily comprises psychotherapy and pharmacological treatment. For treatment-resistant patients, who have not responded to several augmentation or combination treatment attempts, electroconvulsive therapy is the treatment with the best empirical evidence.

In this Primer, we provide an overview on the current evidence of MDD, including its epidemiology, etiology, pathophysiology, diagnosis, and treatment.

[H1]Introduction

Major Depressive Disorder (MDD) is a debilitating disease that is characterized by one ore more discrete depressive episodes of at least two weeks' duration involving clear-cut changes in affect, cognition, and vegetative symptoms. Box 1 describes the current diagnostic criteria and specifiers of MDD according to the Diagnostic and Statistical Manual (DSM) 5th edition (DSM 5), which was released in 2013[1].

After puberty, MDD occurs about twice as often in women than in men[2] and affects in a specific year about 6% of the adult population worldwide[3]. Among all medical conditions, MDD is the second leading cause for chronic disease burden as measured by "years lived with disability"[4]. In addition, MDD is associated with an increased risk of developing medical disorders such as diabetes, heart disease, and stroke[5], thereby further increasing its burden of disease. Furthermore, MDD can itself lead to death by suicide. Many of the 800,000 suicides per year worldwide occur within a depressive episode[6] and depressed patients are almost 20-fold more likely to die by suicide than the general population[7].

The genetic contribution to MDD is estimated between 30-40%, with higher heritability in family and twin-based studies than single nucleotide polymorphism (SNP)-based estimates from genome-wide association studies (GWAS). This suggests that other genetic variables such as rare mutations contribute to MDD risk[8,9]. In addition, environmental factors such as sexual, physical, or emotional abuse during childhood are strongly associated with the risk of developing MDD[10,11]. Most studies so far have typically examined single candidate genes in interaction with environmental factors and have not yielded consistently replicated results. Furthermore, GWAS have so far not revealed consistent and replicated associations

with specific genes[12]. However, environmental influences can affect genomic read-out through the action of epigenetic alterations to produce a depressed phenotype[13].

Despite advances in our understanding of the neurobiology of MDD, an established mechanism that explains all aspects of the disease is unavailable. However, MDD is associated with smaller volumes of brain structures such as the hippocampus as well as changes in either activation or connectivity of brain networks such as the cognitive control network and the affective-salience network[14]. Moreover, alterations in the major neurobiological systems that mediate the stress response are present in MDD including the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system, and the immune system[15].

Both psychotherapy and psychopharmacology are effective in treating MDD; however, about 30% of patients do not remit from MDD, even after several treatment attempts[16,17]. Thus, there is an urgent need to further improve MDD therapy. New developments in psychotherapy include the use of behavioral intervention technologies. With regard to pharmacological approaches, glutamatergic antidepressants such as ketamine are currently under scientific scrutiny.

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

[H1] Epidemiology

[H2] Prevalence and main correlates

A best estimate of the world-wide MDD prevalence comes from the World Mental Health (WMH) Survey, which used similar protocols to assess DSM-IV criteria for MDD in 18 countries among almost 90,000 individuals from every continent.[3] The average 12-month prevalence of MDD was around 6%, in line with estimates from earlier large-scale international studies[18,19]. Lifetime MDD prevalence is typically about threefold higher than the 12-month prevalence, indicating that MDD affects 1 out of every 6 adults at some point in their life[3,18,19]. Although a lifetime prevalence is less reliable and likely suffers from recall bias and underestimation[20,21], it indicates that at least 20% of all persons face MDD during life.

The 12-month MDD prevalence in the WMH Survey ranged from 2.2% in Japan to 10.4% in Brazil (Figure 1). Although estimates varied substantially across countries for reasons that likely involve both substantive and methodological processes, the 12-month MDD prevalence was found to be similar in 10 high-income (5.5%) and 8 low- to middle-income (5.9%) countries, illustrating that MDD is not just a 'modern-world' health condition. Also, the median age of onset, severity, symptom profile and basic sociodemographic and environmental correlates (such as sex, education and life events) of MDD are mostly comparable across countries and cultures[22,23]. However, despite these similarities, a clear-cut discrepancy across countries is present in terms of both the resources and treatments availability for mental health, including MDD. In high-income countries approximately 40-50% of all people with severe MDD do not receive proper treatment[24,25], but in low-income countries fewer than 10% of patients received adequate treatment[24].

Starting after puberty, women have a twofold increased risk of MDD than men[2]. This is mainly due to a higher first occurrence of episodes in women, and not because female sex is associated with longer episode duration, differential treatment response or higher recurrence rates[26,27]. In both sexes, the median reported age of

onset of MDD is around 25 years, and the peak risk period for MDD onset ranges from mid-late adolescence to the early 40s[3]. These findings are in line with observations that, especially in high-income countries, the MDD prevalence generally goes slightly down with age after early adulthood[22,28]. Other consistently reported environmental determinants of MDD in both men and women are the absence of a partner (due to divorce or widowhood) and the experience of recent negative life events such as illness or loss of close persons, financial or social problems and unemployment[3,29]. In addition, a range of childhood adversities including physical abuse, sexual abuse and emotional neglect significantly increases the MDD development risk in men and women. Depressed patients with childhood trauma not only have a more than twofold increased MDD risk, but also higher symptom severity, a poorer course and more treatment non-response[30-32]. Finally, other important determinants of MDD are unhealthy lifestyles, as excessive alcohol use, smoking behavior, a high fat or sugar diet and physical inactivity have been associated with (the onset of) MDD and reversing these unhealthy lifestyles appears to reduce depressive symptoms[33-35].

[H2] Course and public health impact

The course of MDD is pleomorphic, with considerable variation in remission and chronicity. In population-based samples the mean episode duration varies between 13-30 weeks and approximately 70-90% of depressed persons recover within 1 year[36-38]. However, in clinical care settings, the course pattern of patients with MDD is less favorable: only 25% remit within 6 months and >50% of patients are still depressed after 2 years[27,39,40]. After MDD remission, residual symptoms and functional impairment often remain[41]. Also, the chance of MDD recurrence is high, as about 80% of remitted patients experience one or more recurrences during their

lifetime[42]. The course trajectory in adults seems to be slightly less favorable with older age[27] . However, the most important course determinants are clinical characteristics. Higher symptom severity, psychiatric comorbidity and a history of childhood trauma all predict a less-favorable course[27,31].

The Global Burden of Disease Consortium found that, in 2013, MDD was the second leading contributor to global disease burden, as expressed in disability adjusted life years, both in developed as well as in developing countries[4]. Moreover, the consequences of MDD extend to physical health. Large-scale longitudinal studies converge in their findings that MDD increases the onset risk of diabetes, heart disease, stroke, hypertension, obesity, cancer, cognitive impairment and Alzheimer's disease (Figure 2)[43]. Both in the general population as well as in populations with specific medical illnesses, MDD increases the mortality risk by 60–80%[44,45]. Indeed, the contribution of MDD to all-cause mortality is 10%, indicating that mortality rates would decrease by 10% if MDD could be eliminated completely.

[H1] Mechanisms/pathophysiology

Despite advances in our understanding of the neurobiology of MDD, there is currently no established mechanism that could explain all facets of the disease. In box 2, we briefly discuss the potential and the challenges of animal models for MDD and provide recent references that discuss in detail molecular mechanisms of candidate neurobiological systems that have been identified in animal models. In the main text, we largely restrict our discussion to findings in clinical studies of patients with MDD, giving preference to those aspects that have been confirmed in meta-analyses and pathways that have been targeted in clinical trials (ideally also with a meta-analysis level of evidence).

[H2] Genetics

We have known for more than a century that MDD clusters within families. First-degree relatives of patients with MDD show a threefold increased risk of MDD, and heritability for this disorder has been quantified as 30-40%[8]. Furthermore, there is a genetic overlap between MDD and other psychiatric disorders[46,47]. However, the search for main genetic effects in MDD so far has not revealed consistent and replicated genome-wide significant genetic findings for MDD[48] as indicated by a mega-analysis of various GWAS including 9,240 cases and 9,519 controls[49]. Similarly sized studies of other psychiatric conditions such as schizophrenia, which have a higher heritability, have convincingly implicated at least some genetic loci; for schizophrenia, 108 independent genome-wide significant loci have been shown[50]. Risk of MDD is highly polygenic and involves many genes with small effects[51]. Furthermore, the heterogeneity of the depressed phenotype further increases the number of subjects needed to find significant genetic associations. A recent Chinese GWAS in which a more homogeneous phenotypic approach was applied was able to confirm two genome-wide significant genetic loci[52]. This holds promise for some ongoing and soon to be finalized GWAS, which contain increased numbers of depressed cases or focus on huge samples with uniform relevant phenotype information such as depressive symptom reports or neuroticism.

[H2] Environmental factors

Early epidemiological studies focused on stressful events that are temporally related to MDD, usually in the year preceding onset; the primarily documented events (such as loss of employment, financial insecurity, chronic or life-threatening health problems, exposure to violence, separation and bereavement)[53] occur most often

during adulthood. However, more recent evidence has focused on exposure to life events in childhood as antecedent of MDD later in life. These events include physical and sexual abuse, psychological neglect, exposure to domestic violence, or early separation from parents due to death or separation, with clear evidence of a dose–response relationship between number and severity of adverse life events and risk, severity, and chronicity of MDD[11].

A variety of data derived from animal models and clinical research have led to a comprehensive neurobiological model of the long-lasting consequences of early trauma. At the center of this model is the endocrine hypothalamus-pituitary-adrenal (HPA) axis. Many animal studies have demonstrated that early life stress produces persistent increases in the activity of corticotrophic releasing factor (CRF)-containing neural circuits[54]. This finding is paralleled by clinical studies showing that both women and men who have been sexually or physically abused in childhood exhibit, as adults, a markedly enhanced activity of the HPA axis when exposed to standardized psychosocial stressors or following endocrine tests that attempt to suppress HPA activity. Thus, glucocorticoid receptor function is reduced in adult individuals who have experienced childhood adversities (so-called glucocorticoid resistance), a notion that is supported by the fact that these individuals also show increased activation of the inflammatory system, which is under physiological inhibitory control by cortisol. Indeed, glucocorticoid resistance, HPA axis hyperactivity and increased inflammation are all present in MDD (figure 3).

Furthermore, *in utero* stress during the antenatal period has also been shown to increase the risk of MDD later in life[55]. This novel but burgeoning area of research is providing further evidence of the neurodevelopmental origin of MDD and the long-lasting effects of environmental insults at the earliest stages of life[56].

[H2] Gene × environment interactions

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

[H2] Epigenetics

Interestingly, studies investigating the molecular mechanisms underlying G×E interactions have shown that they may involve epigenetic regulation. For example, one polymorphism in *FKBP5* that has been shown to interact with life adversities predicting MDD is associated with allele-specific, stress-dependent DNA demethylation in glucocorticoid response elements[57]. This leads to increased *FKBP5* expression in response to stress, which in turn leads to glucocorticoid receptor resistance, which is often found in MDD[58].

Furthermore, a number of studies have shown consistent epigenetic changes in the brain of animal models of MDD as well as in post-mortem brain samples of depressed patients, especially suicide victims who were exposed to early life adversities[59]. Initial hypothesis-driven studies have examined genes involved in the stress response, but more recent unbiased genome-wide studies have implicated

epigenetic changes in genes often unrelated to established candidates implicating alternative pathophysiological mechanisms, such as cell adhesion and cell plasticity[57]. However, enthusiasm for epigenetic research in MDD is still limited by the small magnitude of the described epigenetic changes, often <10%, especially in comparison with other medical disorders such as cancer[60].

[H2] Neuroendocrinology

The endocrine hypothalamus-pituitary adrenal (HPA) axis is among the most researched biological systems in MDD[61,62]. While the hope for sufficient specificity and sensitivity on an individual level was not met for MDD-specific diagnostic HPA tests[63], evidence suggests that overall HPA axis regulation is altered in patients with MDD. Two meta-analyses[64,65] concluded that cortisol levels in MDD were elevated, with a moderate effect size. Importantly, HPA alterations correlate with impaired cognitive function[66,67] in depressed patients and they are more common and more pronounced in severely depressed patients with melancholic and/or psychotic features[68] and in elderly depressed patients[69]. Furthermore, several studies have prospectively shown that elevated cortisol is a risk factor for subsequent MDD[70-72]. Finally, in a study using data from a primary care database including more than 370,000 individuals indicated that treatment with synthetic glucocorticoids is associated with an increased risk for suicide (approx. 7-fold), MDD (approx. 2-fold) and other severe neuropsychiatric disorders, even when controlling for the underlying medical disorder[73].

Antidepressants reduce cortisol levels in depressed patients over the course of the treatment[74]. However, a meta-analysis has shown that independent of improved psychopathology about 50% of depressed patients had similar cortisol levels before

and after treatment. Elevated CRF in the cerebrospinal fluid (CSF) has been found in patients with MDD[75] and, accordingly, several randomized controlled trials have examined CRF-antagonists in the treatment of MDD. However, the overall results have not indicated a major role for CRF antagonists in the treatment of MDD[76]. Clinical trials using glucocorticoid-lowering compounds such as metyrapone have also yielded mixed results[77,78]. Fludrocortisone, a mineralocorticoid receptor agonist, has been shown to accelerate the onset of action of standard antidepressants in one randomized controlled trial[79] and to improve cognitive function in depressed patients in an experimental study[80]. In psychotic MDD, the glucocorticoid receptor antagonist mifepristone (RU-486) was shown to ameliorate psychotic symptoms, although secondary analyses of failed trials indicated that very high doses might be required to reach therapeutic blood levels[62].

[H2] Inflammation

A role of peripheral immune dysfunction and neuroimmunological mechanisms in MDD has been supported by a large body of evidence from animal studies (box 2). These models have also provided intriguing insights into how peripheral cytokines can, directly and indirectly, affect brain circuits, behavior and mood. Such mechanisms may also underlie clinical observations in MDD: A population-based study has shown that both prior severe infections as well as autoimmune diseases increase the risk of subsequently developing MDD[81]. Patients who receive cytokine treatments such as IL-2 or IFNγ as part of their treatment for hepatitis or cancer often develop depressive symptoms[82]. Finally, patients with MDD show elevated serum levels of tumor necrosis factor (TNF) and IL-6 as confirmed by a meta-analysis[83,84]. Increased expression of genes involved in IL-6 signaling in peripheral blood cells has also been observed in a large-scale cohort study of patients with MDD compared

with healthy controls[85]. There have also been a few large, prospective studies indicating that elevated levels of IL-6 during childhood significantly increase the risk of developing MDD in adulthood[86]. Recent studies using PET imaging[87] as well as analyses of post-mortem brain tissue[88] have indicated neuroinflammation and microglial activation in the central nervous systems of patients with MDD. Finally, a potential role of inflammation in MDD is also supported by clinical trials of nonsteroidal anti-inflammatory drugs (NSAIDs) such as COX-2 inhibitors reviewed by a recent meta analysis[89].

[H2] Neuroplasticity

Peripheral changes in cortisol levels and inflammatory mechanisms induce depressive symptoms by ultimately affecting brain function at a cellular level, primarily by disrupting neuroplasticity. Lower levels of the neurotrophin, brain-derived neurotrophic factor (BDNF), have been found in the serum and in the leukocytes mRNA of depressed patients, and pharmacological and non-pharmacological antidepressant therapies have been found to normalize BDNF levels[90]. BDNF and other components of the neuroplasticity network, affect behavior also by regulating neurogenesis, the process by which new neurons are generated in the adult brain from pluripotent stem cells. The role of neurogenesis in MDD has been amply debated[91]. For example, reducing experimentally adult neurogenesis in rodents in the absence of stress does not induce depressive-like behavior. However, reduced neurogenesis can precipitate depression-like symptoms in the context of stress, probably because it impairs the ability to respond to stress. For example, at a biological level, adult neurogenesis promotes resilience to stress by enhancing glucocorticoid-mediated negative feedback on the HPA axis, and at a cognitive level it influences whether events are perceived as stressful and, therefore, whether a

stress response is elicited. According to the latter notion, reduced neurogenesis results in “overgeneralization”, so that even innocuous stimuli are associated with negative memories and become emotionally charged. This results in a stress response, which is further unrestrained by the lack of the aforementioned neurogenesis-related enhancement of glucocorticoid-mediated negative feedback. In contrast, an effective adult neurogenesis, as occurring following antidepressant treatment, reduces stress responsiveness and maintains resilience[91].

[H2] Monoamines

The monoamine hypothesis of MDD was initially developed based on findings that substances such as the antihypertensive drug reserpine that reduce monoamines such as serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, or dopamine in the synaptic cleft, led to MDD in a subgroup of patients. Furthermore, the first antidepressant drugs were developed in the 1950s, when the antidepressant properties of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were discovered by serendipity. Both TCAs and MAOIs were subsequently shown to have robust effects on monoamine neurotransmission. These findings stimulated the development of a long series of monoamine-based compounds, which have dominated the field of modern psychopharmacology of MDD thus far. For example, the newer selective serotonin reuptake inhibitors (SSRI) strongly bind to the serotonin transporter (5-HTT) with little or no impact on post-synaptic monoamine receptor activity.

However, a plethora of studies that have measured norepinephrine and serotonin metabolites in plasma, urine, and cerebrospinal fluid, as well as postmortem studies of the brains of depressed patients have yielded inconsistent results[92]. Furthermore,

drugs that target monoamines affect these neurotransmitter systems within hours after administration. However, antidepressant effects only occur with a delayed onset of action that can last up to several weeks. Presumably, changes in brain gene expression that occur after continuous treatment with monoaminergic antidepressants might underlie their therapeutic effects[93].

[H2] Structural brain alterations

Many cross-sectional studies using structural brain imaging have investigated regional brain volumes in patients with MDD, which have been summarized in meta-analyses. A meta-analysis of 143 studies[94] confirmed smaller volumes in patients with MDD than in healthy controls in the basal ganglia, thalamus, hippocampus and several frontal regions (Figure 5). A meta-analysis of MRI data from more than a dozen independent research samples by the ENIGMA working group detected significantly lower volumes in the hippocampus (but no other subcortical structures) [95] as well as cortical thinning in the orbitofrontal cortex, anterior and posterior cingulate, insula and temporal lobes in MDD patients [96]. Furthermore, a large scale trans-diagnostic voxel-based morphometry meta-analysis of 193 studies comprising 15,892 individuals also suggested that the hippocampus might be selectively affected in MDD compared to other psychiatric disorders such as schizophrenia, bipolar disorder, addiction, obsessive-compulsive disorder, and anxiety[97]. While an earlier meta-analysis suggested that smaller hippocampal volumes might already be present in patients with first episode MDD[98] this could not be confirmed in the most recent meta-analysis of MRI data by the ENIGMA working group [95]. Thus, it remains unclear whether smaller volumes of the hippocampus seen in MDD are an early manifestation or develop later in the course of the disorder.

[H2] Functional brain circuits

Neuroimaging studies in MDD have identified abnormalities in either activation or connectivity within the affective-salience circuit, the medial prefrontal-medial parietal default mode network and the fronto-parietal cognitive control circuit.

[H3] Affective-salience circuit.

One of the most frequently reported neuroimaging findings in MDD is abnormally increased connectivity and heightened activation of the amygdala[99-101]. Much like the amygdala, the dorsal anterior cingulate and anterior insula are hyperactive in MDD, which may reflect the increased salience of negative information and self-directed thoughts in MDD[101]. By contrast, decreased activity and connectivity of the ventral striatum and other reward-related regions has been found in MDD, leading to decreased recruitment of saliency processing areas like the dorsal cingulate and anterior insula[102-106].

[H3] Default mode network.

The default mode network is characterized by greater activity during “resting” states where most mental activity is internal or self-directed. Difficulties in dynamic modulation of the default mode network in MDD has been proposed to underlie excessive self-focus and rumination[100,107-111]. Indeed, the default mode is hyperconnected in MDD[112-114], which correlates positively with measures of rumination[115,116]. In contrast, the dynamic coupling between frontoparietal activation (which increases with task-directed attention) and default mode deactivation is perturbed in MDD[111,117].

[H3] The fronto-parietal cognitive control circuit.

The fronto-parietal cognitive control network is engaged across many cognitive tasks[118]. A recent meta-analysis found evidence for frontoparietal hypo-connectivity in MDD, especially of the dorsolateral prefrontal cortex, implicating it in goal-directed attention deficits in MDD[119]. Moreover, decreased frontoparietal connectivity has been found both at rest and in response to negative stimuli, but not in response to positive stimuli, suggesting that this network may contribute to inappropriate cognitive appraisals of negative events more specifically[100,105].

[H1] Diagnosis, screening and prevention

[H2] Differential diagnosis

According to DSM 5 (Box 1), MDD is demarcated from normal sadness or bereavement; however, in patients who are mourning who develop symptoms severe enough and persistent beyond the acute grieving period, an MDD diagnosis can be given. While it is possible to diagnose MDD based on a single depressive episode, MDD is recurrent in the majority of cases[1].

The key differential diagnosis of MDD is with bipolar depression and with persistent depressive disorder. The differential diagnosis of MDD from bipolar depression rests entirely with the presence of a history of hypomania or mania, which is characterized by a clear period of elevated mood or irritability and with at least three of the following symptoms presently overtly: inflated self-esteem; reduced need for sleep; increased speech; flight of ideas; distractibility; increased activity in goal-directed tasks; and involvement in risky behavior.

Persistent depressive disorder is a chronic disorder and describes patients who have been depressed for >2 years. Apart from depressed mood, only two of six symptoms (appetite disturbance; sleep disturbance; loss of energy; decreased self-esteem; poor concentration; or hopelessness) are required for the diagnosis. Thus, it is possible to meet criteria for persistent depressive disorder without having MDD. If a patient meets criteria for MDD, then the patient would receive two diagnoses — MDD and persistent depressive disorder.

[H2] Specifiers of MDD

Once a diagnosis of MDD is made, the condition can be further characterized using a variety of modifiers or specifiers (Box 1).

Severity of episode is rated from mild to moderate to severe. Severe symptoms have a major impact on function. The specifier “with anxious distress” was introduced because depressed patients with considerable co-occurring anxiety are more likely to report suicidal thoughts and be less responsive to traditional antidepressants. The specifier requires prominent symptoms of anxiety present most of the days the patient experiences an episode of MDD. Patients are also required to experience at least two of the following: a sense of being keyed up or tense, unusual restlessness, trouble concentrating secondary to worry, fearing awful things will happen, and worry about losing self-control.

The specifier “with mixed features” reflects a notion that MDD lies on a continuum with bipolar disorder and that patients with either can demonstrate features of the other during an index episode[1]. This hypothesis is based on the observation that some depressed patients show rapid thinking and reduced need for sleep. The

criteria include experiencing at least three of the following symptoms during the depressive episode: elevated, expansive mood, heightened self-esteem or grandiosity, increased speech or pressure of speech, racing thoughts, increased energy or directed activity, excessive activity in behavior with possibly negative consequences, or lessened need for sleep.

"With melancholic features" refers to the presence of what has often been called endogenous features. The criteria include anhedonia, lack of pleasure, loss of reactivity to positive stimuli, distinct quality of depressed mood such as despair, depression worse in the morning, waking early in the morning, psychomotor disturbance, weight loss, and excessive guilty thoughts.

The specifier "with atypical features" refers to a set of symptoms that are common in MDD. The criterion in mood reactivity in atypical depression requires that mood brightens in response to actual or potential positive events, which is in contrast to "with melancholic features". Other criteria include at least two out of: significant increase in weight or appetite; increased sleep; a sense of leaden paralysis; and interpersonal sensitivity.

Previously, the "with psychotic features" specifier in DSM-IV was included as part of the severity continuum from mild to severe with psychotic features. In DSM-5, psychotic features were separated from the severity specifier because the two were not always highly correlated (that is, mild MDD can also present with psychotic features)[120].

The specifier "with catatonic features" refers to "marked psychomotor disturbance that may involve decreased motor activity, decreased engagement during interview or physical examination, or excessive and peculiar motor activity (DSM 5). These patients are often psychotic.

[H2] Research Domain Criteria (RDoC)

In addition to DSM-5, the National Institute of Mental Health (NIMH) developed research domain criteria (RDoC), which are not meant to be a diagnostic system but a framework for organizing research. The RDoC approach consists of a matrix where the rows represent specified functional constructs characterized by genes, molecules, cells, circuits, physiology, self-report, and paradigms used to measure it (https://www.nimh.nih.gov/research-priorities/rdoc/development-and-definitions-of-the-rdoc-domains-and-constructs.shtml.). Constructs are in turn grouped into five higher-level domains of functioning (negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems). The ultimate goal of RDoC is to develop a deeper understanding of the biological and psychosocial basis of psychiatric disorders, which might help to improve current classification systems [121].

[H2] Screening

Screening is discussed controversially in the MDD field. Many experts argue that screening for depression is of obvious benefit since MDD is often overlooked in medical settings[122,123]. In contrast, other authors state that it is impractical to implement universal screening and argue that there is a lack of evidence supporting screening[124]. A recent systematic review included 71 studies and assessed benefits and harms of screening for depression in primary care[125]. The authors concluded that the overall evidence of health benefit of depression screening in primary care is

weak. However, the existing data do suggest that screening programs generally increase the likelihood of remission and treatment response in general adult populations but only in the presence of subsequent treatment offers.

[H2] Prevention

Given the high prevalence of depression, effective prevention strategies such as strengthening protective factors (such as increasing social support or problem-solving skills) or diminishing prodromal disease stages (such as reducing depressive symptoms that do not fulfill criteria for MDD yet) might have an enormous public health impact in reducing disease burden. The effects of preventive psychological interventions on the incidence of MDD have been systematically examined in a meta-analysis of 32 randomized controlled trials. The meta-analysis included studies examining universal prevention (in a whole population group regardless of risk status), selective prevention (in individuals or subgroups that are at higher risk of developing depression) and indicated prevention (in individuals who are identified as having prodromal symptoms of depression, but who do not yet meet the diagnostic criteria for a full-blown MDD diagnosis).

The results indicated a 21% decrease in incidence in prevention groups in comparison with control groups[126]. The authors concluded that prevention of depression seems feasible and may be an effective way to reduce the numbers of incident MDD cases.

[H1] Management

[H2] Psychotherapy

Psychotherapy for depression comes in many different forms, the most common of which are described in Box 4. These different paradigms rely on different conceptual models and prescribe techniques that vary to some degree in their focus and methods. A large number of randomized controlled trials and meta-analyses consistently show that psychotherapy is effective at treating depression, and that there are no consistent or clinically meaningful differences between different types of psychotherapy[127-129] .

This conclusion[130] has led to two broad hypotheses. The first, the non-specific or common factors explanation, argues that the primary agents for change in psychotherapy are largely those that are common to all psychotherapies, such as the therapeutic alliance (a positive, warm, caring and genuine stance)[131] and therapist factors[132], which are common to all forms of psychotherapy. The common factors approach would suggest that focusing training and quality assurance on these common factors can optimize treatment outcomes.

By contrast, proponents of the specific-factors explanation argue that treatment-specific strategies produce change via different pathways, such as cognitive restructuring, behavioral activation, or improved interpersonal functioning[133]. Accordingly, head-to-head comparisons of different psychotherapeutic treatment models, which are grossly underpowered to detect treatment differences[134], hide patient variables such as severity of depression, social dysfunction, cognitive dysfunction, which have been shown to differentially predict outcomes to different treatment modalities[135,136]. To the degree that the specific factors hypothesis is true, treatment outcomes may be optimized by tailoring specific interventions to patient characteristics.

Psychotherapy produces effects that are largely equivalent to pharmacotherapy although effect sizes from pharmacological and psychotherapeutic trials cannot be readily compared due to methodological issues (e.g. blinding)[137]. A recent individual patient data meta-analysis, combining the data across 16 trials comparing individual psychotherapy to antidepressant medication, found no meaningful differences in outcomes on self-reported depression, or rates of response or remission[138]. The beneficial effects of cognitive therapy have been shown to persist for at least one year post-treatment, similar to keeping people on antidepressant medications, and with lower relapse rates compared to patients who withdraw from medications [139].

Although psychotherapy is clearly effective, large numbers of people have access barriers, including time constraints, lack of available services, and cost [140,141]. Providing psychotherapy over the telephone has been repeatedly shown to be an effective medium for delivering psychotherapy[142], producing outcomes that are equivalent to face-to-face therapy and reducing dropout[143]. Furthermore, group therapy is often recommended as a less-costly way of providing treatment, particularly for patients with mild to moderate levels of symptoms[144]. Trials comparing individual to group psychotherapy have shown individual treatment to be moderately superior to group at post-treatment, however these differences disappear at 3-month follow-up[145].

[H2] Behavioral intervention technologies

Behavioral intervention technologies, which use computers, tablets, and phones to teach self-management skills[146], are effective at reducing symptoms of depression, when applied correctly. While standalone technology-based interventions have not shown consistent benefits, primarily because people with depression do not

adhere to them, internet-based tools, combined with low-intensity coaching via phone or messaging, are highly effective at reducing symptoms of depression[147,148]. Evidence for the efficacy and cost-effectiveness of these coached intervention technologies has led to their being integrated into national mental health services in a number of countries, including England[149] and Australia[150].

However, well-designed head-to-head comparisons of technology-supported care and more traditional forms of psychotherapy and pharmacotherapy have yet to be conducted. It is unclear if there are differences in who might respond to technology-based treatments relative to traditional treatments, and indeed, as attitudes and expectations about the role of technology in daily life change, the populations that are responsive to such treatments will likely change. The rapid rate at which technology advances means that technology-based interventions will continue to proliferate and evolve rapidly[151].

An emerging area of technology is digital phenotyping, which harnesses the growing availability of data generated continuously in the course of daily lives to create behavioral markers related to depression. For example, mobile phones, with a growing complement of sensors, have become personal sensing systems. Because people tend to keep their phones with them, phone sensors can continuously estimate severity of depression in real time[152]. This opens the possibility of intervention tools that can detect and react to sensed states and behaviors, allowing just-in-time prompting and reinforcement of treatment congruent behaviors [153], as well as tools that can passively monitor risk of depression. Harnessing personal sensing platforms such as mobile phones and wearables has the potential to shift our treatment tools from episodic to continuous, from reactive to proactive, and from provider-centered to patient-centered [154].

[H2] Pharmacotherapy

Three decades after the “monoamine hypothesis of depression” emerged, it became clear that this hypothesis was overly simplistic and that the modulation of monoamines by antidepressants was only an initiating event[155].

[H3] Mechanisms of action

The actual therapeutic actions of monoamine-based antidepressant drugs are thought to result from slower adaptive neuronal responses to these initial biochemical perturbations. Downstream intracellular signal changes pathway as well as changes in gene expression and neural and synaptic plasticity including hippocampal neurogenesis may actually play a critical role in antidepressant drug action[156,157 158].

All these research findings put into question the usefulness of the standard classification of antidepressant drugs, typically based on the specific effects on monoamines. However, such classification, often reflecting the affinity of drugs for pre- and post-synaptic monoamine receptors and/or monoamine transporters, has been useful in understanding some of their side effects. Recently, a new initiative from five international scientific organizations with focus and expertise in neuropsychopharmacology developed a “neuroscience-based nomenclature”[159,160] of psychotropic drugs that organizes medications based on their known pharmacologic actions as opposed to grouping them according to indications (“antidepressants”, “antipsychotics”, etc.).

The selective serotonin reuptake inhibitors (SSRIs) (such as fluoxetine, sertraline, paroxetine, citalopram, escitalopram and fluvoxamine) have shown at therapeutically

relevant doses to have significant binding to the serotonin transporter (5-HTT) and are typically devoid of post-synaptic monoamine receptor activity. Vilazodone, has significant affinity for serotonin 5-HT1A receptors as well as for the 5-HTT. The relatively selective norepinephrine reuptake inhibitors (NRIs) (such as reboxetine) have also shown at therapeutically relevant doses to have significant binding to the norepinephrine transporter without any significant post-synaptic monoamine receptor activity. The TCAs and other cyclic antidepressants, as well as the serotonin norepinephrine reuptake inhibitors (SNRIs) block the reuptake of norepinephrine serotonin by binding to their transporter in varying ratios. All the available SNRIs (venlafaxine, duloxetine, desvenlafaxine, milnacipran and levomilnacipran) share the property of being potent inhibitors of serotonin and norepinephrine uptake, with minimal or no affinity for postsynaptic receptors, with the exception of venlafaxine, which acts as a mild antagonist of nicotinic acetylcholinergic receptors.

By contrast, TCAs, to varying degrees, are potent blockers of histamine H-1 receptors, serotonin 5-HT2 receptors, muscarinic acetylcholine receptors, and α1-adrenergic receptors. These effects account for the higher degree of side-effect burden of the TCAs compared to the other classes of antidepressants. The norepinephrine dopamine reuptake inhibitors (NDRIs) such as bupropion primarily block the reuptake of dopamine and norepinephrine and have minimal or no affinity for post-synaptic receptors. The α2-adrenergic receptor antagonists (such as mirtazapine and mianserin) seem to enhance the release of both serotonin and norepinephrine by blocking auto- and hetero-α2 receptors. Given mirtazapine's antagonism of serotonin 5HT2 and 5HT3 receptors, it has been argued that its overall effect is an enhancement of 5HT1A-mediated serotonergic transmission and of norepinephrine release, in addition to blocking histaminergic H-1 receptors. The

latter effect is thought to be responsible for significant sedation. Mianserin is also a 5HT2 antagonist. More selective serotonin receptor antagonists/agonists (such as nefazodone and trazodone) primarily bind to serotonin 5-HT2 receptors. Vortioxetine, has significant affinity for serotonin 5-HT1A, 5-HT1B, 5-HT1D, 5-HT3, 5-HT7 receptors as well as for the 5-HTT. Agomelatine is a melatonin receptor (MT1 and MT2) agonist and a 5-HT2c antagonist without anticholinergic or antihistaminergic properties.

Most currently used MAOIs (such as isocarboxazid, phenelzine, tranylcypromine, and selegiline) are irreversible inhibitors of both MAOA, preferentially oxidizing serotonin, and MAOB, preferentially oxidizing phenylethylamine (PEA) and benzylamine, with dopamine, tyramine, and tryptamine being substrates for both forms of MAO. Moclobemide is a selective and reversible MAOA inhibitor.

[H3] Tolerability and efficacy

The success of the SSRIs and SNRIs in displacing tricyclic drugs as first-choice agents is not based on established differences in efficacy, but rather on a generally more favorable side effect profile such as lack of anticholinergic and cardiac side effects, a high therapeutic index (ratio of lethal dose: therapeutic dose), combined with ease of administration. However, all the monoamine-based antidepressant drugs, regardless of their pharmacological class, have fundamentally comparable modest efficacy, with response rates hovering around 50%, and exhibiting a characteristic delayed (typically over several weeks) response to treatment[16,161].

Drugs such as the SSRIs and SNRIs are also not devoid of significant tolerability issues: common acute treatment side effects are nausea, insomnia, headaches,

dizziness, gastrointestinal symptoms, and sexual dysfunction, whereas their common long-term side effects include weight gain, sexual dysfunction, and sleep disturbances[162]. In the past two decades, there have been significant efforts to develop antidepressant drugs that are not monoamine-based, that are devoid of some of the untoward side-effects of these drugs, and that are capable to induce clinical changes in a much more rapid fashion. Compounds that are under development include neurokinin NK-1 antagonists[163], glutamatergic system modulators[164], anti-inflammatory agents[165], opioid tone modulators and opioid kappa antagonists[166], hippocampal neurogenesis-stimulating treatments[167], and antiglucocorticoid therapies[168]. The degree of advancement in the development process varies across these different mechanisms, although all of these types of compounds have shown some degree of promise in the treatment of MDD.

[H2] Combined pharmacotherapy and psychotherapy

A number of studies have shown that initiating treatment with both psychotherapy and pharmacotherapy produces significantly better outcomes than either treatment alone[169,170]. Similarly, augmenting psychotherapy or antidepressant medications with the treatment not received when the monotherapy has not achieved satisfactory results is also effective at increasing the response rate[171].

[H2] Treatment-resistant depression

The term treatment-resistant depression (TRD) is typically used to describe a form of MDD that has not responded adequately to at least one antidepressant trial of adequate doses and duration[172] although varying definitions of treatment resistance exist[173]. TRD is frequently observed in clinical practice, with up to 50%-60% of

patients not obtaining adequate response following antidepressant drug treatment[172]. A careful diagnostic re-assessment is considered critical to the proper management of TRD patients (Figure 6). More specifically, it is important to evaluate the potential role of several contributing factors, such as medical and psychiatric comorbidity. The degree of resistance to treatment can vary greatly among TRD patients and some staging methods to classify TRD based on different levels of treatment resistance have shown to be of utility clinically[174]. A recent meta-analysis found several variables to be associated with treatment resistance including older age, marital status, longer duration of current depressive episode, moderate to high suicidal risk, anxious comorbidity, higher number of hospitalization, and comorbid personality disorders[175].

There are multiple general approaches to TRD. The most established strategies include psychopharmacological approaches, psychotherapy and electroconvulsive therapy.

[H3] Psychopharmacological strategies.

The term optimization/high dose refers to a psychopharmacological strategy involving the significant increase of the dose of the antidepressant in the face of non-response (e.g., doubling or tripling the dose), strategy that has been shown to lead to significant improvements, particularly in the event of partial response[176]. This has recently been confirmed in two meta-analyses for SSRI[177,178].

The psychopharmacological strategy of switching involves changing the primary antidepressant drug to another of the same class or of a different class. In the STAR*D study, this strategy has been shown to lead to remission in one of four patients in citalopram non-responders (both within the same class or with a different

class), but its success in patients who have not responded to two antidepressant trials is extremely modest, with remission only in one of ten patients[16].

The psychopharmacological strategy of augmentation refers to the addition to ongoing antidepressant drug treatment of drugs that are not antidepressant agents themselves. Initially well-studied augmentation strategies such as lithium or L-triiodothyronine (T3)[179] have become somewhat less common in practice, while augmentation with atypical antipsychotic drugs such as quetiapine or aripiprazole is increasingly established[180].

Combination treatment generally refers to the prescribing of more than one antidepressant simultaneously. The array and number of combinatory possibilities has dramatically increased with the introduction of newer antidepressant agents. The two best studied combination strategies, studied in STAR*D as well, are SSRIs/SNRIs with bupropion or mirtazapine[16].

[H3] Psychotherapy.

In TRD, the most commonly used form of psychotherapy studied is cognitive behavioral therapy. A systematic review of the pertinent literature concluded that the current evidence examining the effect of psychotherapy as augmentation or substitute therapy in TRD is sparse and reveals mixed results[181]. However, the use of cognitive behavioral therapy in citalopram non-responders of the STAR*D study was associated with comparable efficacy to pharmacotherapy[17]. Furthermore, a recent large-scale randomized controlled study has demonstrated both efficacy and long-term effectiveness of cognitive behavioral therapy as adjunct to pharmacotherapy in treatment-resistant depression[182,183]. Finally, a recent meta-analysis has demonstrated efficacy for the cognitive behavioral analysis system of

psychotherapy (CBASP), a specific psychotherapy for chronic depression including treatment resistant depression[184].

[H3] Electroconvulsive therapy.

Electroconvulsive therapy (ECT) is considered to be the most widely used and effective non-pharmacological biological treatment for TRD[185]. It is commonly used when a rapid antidepressant response is required, such as in very severely depressed and/or highly suicidal patients. The main tolerability issues of ECT are its cognitive side effects, especially anterograde and retrograde amnesia. It appears that right unilateral ECT is as effective as bilateral treatment, albeit bilateral treatment may lead to more rapid clinical response. Another approach is to use ultra-brief pulse-width (UBP) stimulation in order to minimize cognitive side effects. However, a systematic review found that, UBP ECT may yield lower efficacy as well as lower speed of remission[186] .

[H3] Emerging treatments.

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

A recent review of 18 TRD studies of rTMS concluded that, for MDD patients with 2 or more antidepressant treatment failures, rTMS is a reasonable, effective

consideration[187]. However, a meta-analysis has shown that rTMS is inferior to ECT with regard to efficacy in TRD[188].

In contrast to standard TMS, deep TMS (dTMS) modulates neuronal activity in deeper regions of the brain.. A recent review concluded that dTMS in TRD patients is effective both as a monotherapy and as an add-on treatment[189].

Magnetic seizure therapy (MST) combines elements of both rTMS and ECT. In MST, a rTMS device is used to induce a seizure, with the procedure being otherwise conducted as ECT using a general anaesthetic and a muscle relaxant. A review of eight MST studies reported remission rates ranging from 30% to 40%, and no significant cognitive side effects related to MST[190].

Transcranial direct current stimulation (tDCS) typically applies a weak direct current via scalp electrodes overlying targeted cortical areas[191]. A recent review concluded that the data do not support the use of tDCS in TRD[192].

Low field magnetic stimulation (LFMS) refers to a form of brain stimulation delivered in a magnetic field waveform inducing a low, pulsed electric field in the brain. Two sham-controlled pilot studies of LFMS have shown a rapid antidepressant effect in mood disorder patients[193].

Vagus nerve stimulation (VNS) involves the surgical implantation of a pacemaker-like pulse generator in the chest, connected to a stimulating electrode attached to the vagus nerve in the neck. VNS results in activation of a variety of subcortical brain structures and the stimulation of hippocampal neurogenesis[194]. Despite the fact that the only controlled trial in TRD of VNS using a sham control did not achieve the pre-specified statistical significance and reported modest response rates in the acute

phase, long-term, extension phases of VNS treatment have been associated with an increased therapeutic effect over time, with a sustained response rate of 40% and a remission rate of 29% after a 9 month follow-up[194].

Deep brain stimulation (DBS) involves the implantation of a pulse generator connected to two stimulating electrode wires, surgically placed in specific brain regions. As pointed out by Fitzgerald[195], DBS is typically reserved for patients with the most severe forms of TRD, and requires further evaluation of both administration methods and its role in MDD therapy.

A novel pharmacological approach to the treatment of TRD involves parenteral or intranasal administration of the glutamergic drugs ketamine and esketamine. A review of 21 studies found that single ketamine intravenous infusions elicit a significant antidepressant effect from 4 h to 7 days in TRD patients[196]. Similar results were reported in a trial of a single intravenous infusion of esketamine[197]. Other drugs with NMDA receptor antagonism properties have been associated with relatively more modest antidepressant effects compared with ketamine; however, they have shown other potentially favorable characteristics, such as decreased dissociative or psychotomimetic effects[198]. Other emerging pharmacological augmentation strategies use compounds such as s-adenosyl-methionine[199], l-methylfolate[200], omega-3 fatty acids[201], i.v. scopolamine[202] and the opioid modulator ALKS 5461[203], but their efficacy is not well established yet.

[H1] Quality of life

[H2] Impact on work and family life

Much of the burden of disease associated with MDD is related to the dramatic effect

of MDD on ability to work and the significant strain on family life. In a large survey conducted in the United States, MDD was associated with 27.2 workdays lost per affected worker per year[204].

Epidemiological studies have indicated that low socioeconomic status is linked to MDD[205]. Of particular concern is that MDD has been linked to lower educational attainment [205]. The cause-effect of this association, however, is unclear and a large recent study with 25.000 subjects suggested that it might in part be due to shared genetics[206].

[H2] Cognitive impairment

Considerable literature has supported the presence of objectively measured cognitive deficits in patients with MDD. These deficits affect a wide range of cognitive domains including both “hot” (i.e. emotion-laden) and “cold” (non-emotional) cognition. One meta-analysis identified executive function, memory, and attention as the predominantly affected domains[207]. An attentional bias towards negative information has also been meta-analytically confirmed[208]. Impairments in psychomotor speed, attention, visual learning and memory as well as executive function can already be detected with small to medium effect sizes during a first episode of MDD.[209]

Although the cognitive deficits are more modest after remission (i.e. in euthymic patients with MDD), slight impairments in executive control[207,210] and memory[207] may remain, suggesting that these deficits are not simply an epiphenomenon of decreased motivation during episodes of low mood.

Cognitive impairment in MDD in part depends on the patient subgroup studied. MDD severity, for example, has been shown to be a significant predictor of cognitive dysfunction[211]. In addition, patients with psychotic depression have been shown to

perform significantly worse than patients with non-psychotic MDD on tests of verbal learning, visual learning, and processing speed[212]. Neurocognitive impairment is a relevant factor in patients' quality of life as it is negatively associated with psychosocial functioning in MDD[213]. Overall, antidepressant pharmacotherapy appears to significantly improve cognitive function[214].

[H2] Suicide risk

The most immediate clinical concern with MDD is its strong relation to suicidal intent and completed suicide[215]. Patients with MDD have a 1.8 fold increased overall mortality and MDD patients lose an estimated 10.6 life years lost for men and 7.2 years for women[7]. This is due – in part – to the elevated risk of suicide in this population. In a meta review, the risk of suicide in MDD was almost 20 fold higher than in the general population[7].

The effectiveness of behavioral and psychosocial interventions to prevent suicide and suicide attempts has been supported by a recent meta-analysis, particularly for interventions that directly address suicidal thoughts[216]. There are also strategies to reduce suicides at "suicide hotspots" (i.e. public areas often used for suicides) that aim at restricting access to means and encouraging help seeking that might be effective according to one meta analysis[217].

It should be noted that recent meta-analyses of randomized controlled trials have not found a beneficial effect of antidepressants to reduce suicide risk in MDD[218,219]. Importantly, risk and benefit of antidepressants use and suicidality appear to be strongly age dependent[220,221]. Meta-analyses revealed that suicidal ideation or behavior associated with antidepressants was non-significantly increased in patients < 25 years, non-significantly decreased in patients 25 – 64 years and highly significantly decreased in patients > 64 years (OR 0.37, 95% CI 0.18 to 0.76). In

any event, clinicians should pay special attention to suicidal ideation and suicidality in patients with MDD in general and during antidepressant pharmacotherapy[222].

[H1] Outlook

A pivotal task in the future of MDD research will be to break down the heterogeneous clinical picture of MDD as a broad DSM-5 category into more narrowly defined disease entities with a more specific biology. The initial goal of DSM-5 was to define psychiatric diagnoses including MDD by genetics, neuroimaging, and other biological measures. However, this knowledge has not sufficiently evolved yet to reliably base psychiatric diagnoses on biological measures. Nevertheless, DSM still provides clinicians and researchers with the opportunity of defining subtypes of MDD by grouping patients according to distinct clinical characteristics (for example, melancholic versus atypical depression). Importantly, these subtypes have already been associated with different neurobiological signatures[43]. Furthermore, the concepts of “vascular depression” [223], „metabolic depression“ [224,225], or „inflammatory depression“ [226] that all imply a specific etiology and potentially specific treatments warrant further validation.

Once valid MDD subtypes have been found, it is hoped that these will lead to more specific treatments with better outcomes. There are now several studies that were able to predict response to specific psychological or pharmacological treatment by clinical criteria such as history of childhood trauma[227], neuroimaging markers such as insula hypometabolism[228], or inflammatory markers such as C-reactive protein[229,230]. However, clinical subtypes (melancholic, atypical, anxious) did not predict treatment response in the iSPOT-D and STAR*D trial[231]. Ideally, precision psychiatry will allow

to categorize MDD subtypes in the future analogue to the field of oncology that has started to define different forms of cancer in the same organ into separate disease entities requiring different treatment[232]. It remains to be seen whether the dimensional approach of the RDoC using concepts from genetics as well as from cognitive, affective, and social neuroscience will achieve this goal. It has been argued that the RDoC approach disregards the distinction between “sick” and “well” and that RDoC might introduce a gap between clinicians using DSM-5 and researchers using RDoC[233]. In any event, further research should test the validity of the new DSM 5 specifier with mixed features. A pressing clinical question is whether MDD with mixed features requires a different therapy than MDD without mixed features.

Clearly, MDD is not just a phenomenon in industrialized countries but will affect one out of six individuals worldwide. Therefore, to improve the outcome of MDD treatment worldwide, one of the highest priorities in the field should be to implement effective treatment in low-income countries in which <10% of depressed patients get adequate treatment[234,235]. The currently ongoing mental health Gap Action Programma (mhGAP)[236] of the World Health Organization is aiming to scale up services for mental disorders for countries with low and lower middle incomes. An epidemiological phenomenon consists in the repeatedly described sex differences in prevalence rates of MDD[2] and it will be important to examine the mechanisms that are responsible for the increased MDD prevalence in women.

Given the fact that MDD is a strong risk factor for developing metabolic and cardiovascular diseases and for a worse course and outcome in these diseases[5], it will be important to learn more about the mechanisms of association between MDD

and other medical diseases such as diabetes or coronary heart disease. Future research should also examine whether treatment of comorbid MDD reduce morbidity and mortality in medical patients.

In terms of the etiology and pathophysiology of MDD, many questions remain unresolved. For example, how exactly is the immune system dysregulated in MDD (i.e. which immune compartment (innate vs. adaptive immunity) is affected? Again, are immunological alterations present in MDD in general or only in specific subtypes? Furthermore, there is a lack of replicated findings in both GWAS and G×E studies[8]. Thus, a crucial question remains how exactly environmental influences interact with the genome leading to MDD. Furthermore, how stable are epigenetic alterations of genomic read-out and are they reversible with successful therapy?

Better treatment for patients is the ultimate goal of all biomedical research and obviously this is true for MDD research as well. In terms of new psychotherapeutic approaches, the technological revolution with its fast evolving developments will allow technology-supported diagnostic and treatment options. This might include intervention tools that can detect and react to sensed states and behaviors, allowing just-in-time prompting and reinforcement of treatment congruent behaviors[153], as well as tools that can passively monitor risk of MDD.

Within pharmacological research, antidepressants within the glutamatergic system such as ketamine are currently under intense scientific scrutiny. An almost revolutionary approach might consist in substances that stimulate neurogenesis in humans. A first phase 1b clinical study has been published in depressed patients demonstrating efficacy compared to placebo in two out of four MDD outcome

measures[167]. However, future studies are necessary to determine safety and efficacy of substances that stimulate neurogenesis in depressed patients.

Perhaps, MDD affects the “conditio humana” more than every other medical disease and its etiology and pathophysiology remains a complex puzzle. Consistent with Winston Churchill’s famous quote “ Success is not final, failure is not fatal: it is the courage to continue that counts“, it will be worth every effort to relieve the enormous burden of MDD.

Box 1. Definition of Major Depressive Disorder according to DSM5

- Five (or more) of the following symptoms have been present during the same 2- week period and represent a change from previous functioning:
    - Depressed mood
    - Markedly diminished interest or pleasure in all, or almost all, activities
    - Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day.
    - Insomnia or hypersomnia nearly every day.
    - Psychomotor agitation or retardation nearly every day
    - Fatigue or loss of energy nearly every day.
    - Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
    - Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
    - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

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

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

- The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

- There has never been a manic episode or a hypomanic episode.

Specifiers of MDD according to DSM-5 are:

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

Box 2. Pathophysiology: from mice to man

Research into the underlying mechanisms of human disorders can be facilitated by model systems that allow reduction and molecular dissection of specific pathways. Finding the appropriate model systems for a given human disease is always challenging. This is particularly true for psychiatric disorders (see [237] for a review). Developing animal models is further complicated by the lack of consistently identified genetic cause of depression in humans. Moreover, many of the symptoms typically seen in patients with MDD are highly subjective (e.g. depressed mood) and only few can be observed and assessed in animals.

Despite these challenges, animal models have allowed the discovery of many exciting target pathways that may contribute to the etiopathogenesis of depression and carefully unraveled the molecular processes involved. These include

- neuroendocrine and -immune mechanisms (see [238-240]),
- epigenetics[241],
- molecular networks and the transcriptome[242],
- the microbiome and the gut-brain axis[243],
- synaptic dysfunction and plasticity[244],
- neurogenesis[245],

Surely, this is a fascinating and highly active area of investigation that has the potential to discover novel targets for therapy and ultimately to bring about better treatments for patients. However, to review all of these in detail would be beyond the scope of this review and reviewing them briefly would not do them justice. Moreover, at present, the clinical relevance of any of these mechanisms for MDD remains uncertain and no newly developed, hypothesis-driven therapeutic approaches for depression have made it to the clinic (yet).

Box 3. Social determinants of MDD (modified after[234])

Several types of social determinants are associated with the risk and outcome of MDD[246]. They can be categorized as follows:

- *Demographic factors:* e.g. age, sex, and ethnicity
- *Socioeconomic status:* e.g. poverty, unemployment, income inequality, low education
- *Neighborhood factors:* e.g. inadequate housing, overcrowding, neighborhood violence and safety
- *Socio-environmental events:* e.g. natural disasters, war, conflict, migration, discrimination, difficulties in work, low social support, trauma, negative life events

There is a bidirectional association between these social determinants and MDD: certain social variables such as low socioeconomic status or lack of social support may contribute to the risk for MDD („social causation“). On the other hand, patients with MDD, especially those with a chronic course of the disease, often deteriorate in their social functioning leading to work and family problems („social drift“), which may eventually lead to poverty[234,246]

Box 4. Psychotherapy for MDD

Cognitive therapy

Cognitive therapy teaches the patient to identify negative, distorted thinking patterns that contribute to depression and provides skills to test and challenge these negative thoughts, replacing them with more accurate, positive ones.

Behavioral activation therapy

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

Psychodynamic therapy

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

Problem solving therapy

Problem solving therapy teaches patients a structured set of skills to generate creative methods of addressing problems, identifying and overcoming potential barriers to goals, and making effective decisions.

Interpersonal therapy

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

Mindfulness-Based Therapy

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

Figure 1. Average 12-month prevalence of major depressive disorder. Although considerable variation in inter-country prevalence is noted, the overall estimates in high-income countries (5.5%) and low- and middle-income countries (LMICs; 5.9%) are not different. Data derived from the World Mental Health Survey[3].

Figure 2. The somatic consequences of major depressive disorder. Evidence from meta-analyses[43] of longitudinal studies have revealed the relative risk (RR) of various diseases is increased in those with major depressive disorder (MDD) compared with those who do not have MDD. The mechanisms contributing to the diverse somatic consequences of MDD are diverse and together may explain the unfavorable health outcomes in depressed patients. They include unhealthy lifestyle, poorer (self)care adherence, medication side effects, shared pathophysiology including e.g. upregulation of immune-endocrine stress systems and genetic pleiotropy (see [39, 247] for a review that gives more details).

Figure 3: Neurobiological systems involved in MDD pathology. Biological alterations associated with MDD have been described in the central nervous system (CNS), the major stress responses systems such as the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system and the immune system. While the sequence of events leading to these changes and their exact interrelation is not known, it is assumed that a combination of vulnerability factors and environmental triggers are the primary event. Psychological stressors set off responses in the HPA axis, which over time show a diminished feedback inhibition capacity resulting in chronically elevated levels of stress hormones such as cortisol and CRH. Chronically elevated stress hormones can also contribute to pathology in cardiovascular and metabolic systems, which often co-occur with MDD. In addition, chronic activation of innate immune responses and elevated circulating levels of inflammatory mediators such as cytokines have been described in MDD; which may be related to a higher incidence of infections in this population. While the cause-effect relationship between these biological correlates is often unclear in clinical studies, mechanistic studies in animals have shown that stress response systems as well as immune activation can directly and indirectly impact on the CNS. Here, they contribute to altered plasticity, connectivity and neurotransmission and may even exacerbate tissue loss. Ultimately, these may underlie abnormal structural and functional connectivity of relevant brain circuits and regional brain volume changes seen in neuroimaging studies.

Abbreviations: ACTH: adrenocorticotropin; CRH: corticotropin releasing hormone; CNS: central nervous system; HPA: hypothalamic-pituitary-adrenal axis; MDD: major depressive disorder; NK: natural killer; IL-6: interleukin 6; IL 1ß: interleukin 1ß.

Figure 4. Model of gene × environment interactions leading to major depressive disorder. The schematic depicts a model of MDD that is based on predisposing genetic vulnerability that interacts with aversive and protective environmental factors in the development of MDD. At least some of the environmental effects are mediated through epigenetic mechanisms to produce the phenotype of MDD, which is characterized by alterations on a molecular level, on a brain network level, and on a behavioral level.

Figure 5. Structural brain alterations in MDD. Regional brain volumes as determined by structural MRI have been investigated in patients with MDD compared to healthy controls in numerous cross-sectional studies. Brain areas with smaller volumes in MDD compared to healthy controls as confirmed in a meta-analysis include the basal ganglia, the thalamus as well as the hippocampus and frontal regions, typically with moderate effect sizes (left panel) and volume differences between 3,5-15.5% (right panel) (based on Kempton et al. [94]). Smaller volumes in the basal ganglia and the hippocampus were also found when comparing patients with MDD and bipolar disorder (based on Kempton et al. [94]), suggesting some specificity for these areas for depressive symptoms occurring in the context of unipolar MDD. Finally, in an independent meta-analysis of structural MRI studies using voxel-based morphometry, only smaller volumes in the hippocampus were specific to patients with MDD when compared to other psychiatric disorders such as bipolar disorder (BPD), schizophrenia (SCZ), anxiety disorders (ANX), obsessive-compulsive disorder (OCD) and substance abuse. *Volume group differences, effect sizes and confidence intervals of MDD compared to healthy controls taken from Kempton et al. [94]). [a] Smaller volumes detected in MDD compared to patients with bipolar disorder. [b] Smaller volumes detected in MDD compared to patients with other psychiatric disorders (SCZ, BPD, substance abuse, OCD, ANX).

Figure 6. Treatment recommendations after a first antidepressant has failed. In patients not responding to an initial treatment with an antidepressant, one or several of the following strategies should be used in parallel including reassessing the comorbid psychiatric and/or medical diagnoses, discussing potential problems with adherence and considering several additional treatment options. The latter can be added at all treatment levels. If still no response occurs, one out of three different pharmacological strategies are recommended: switching the antidepressant, combining two antidepressants, or augmenting the antidepressant with an atypical antipsychotic or lithium. If all of these strategies have failed, electroconvulsive therapy (ECT) is recommended. In a next step, more experimental treatment options with less evidence can be considered such as pharmacological treatment with ketamine or stimulatory treatment with repetitive transcranial magnetic stimulation among other more experimental options (see text).

These are modified recommendations based on three different guidelines: the revised 2015 German national treatment guideline[248] the revised 2015 British Association for Psychopharmacology guideline[78], and the 2010 practice guideline for the treatment of MDD by the American Psychiatric Association[249]. AD = antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and noradrenaline reuptake inhibitor.

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Figure 1

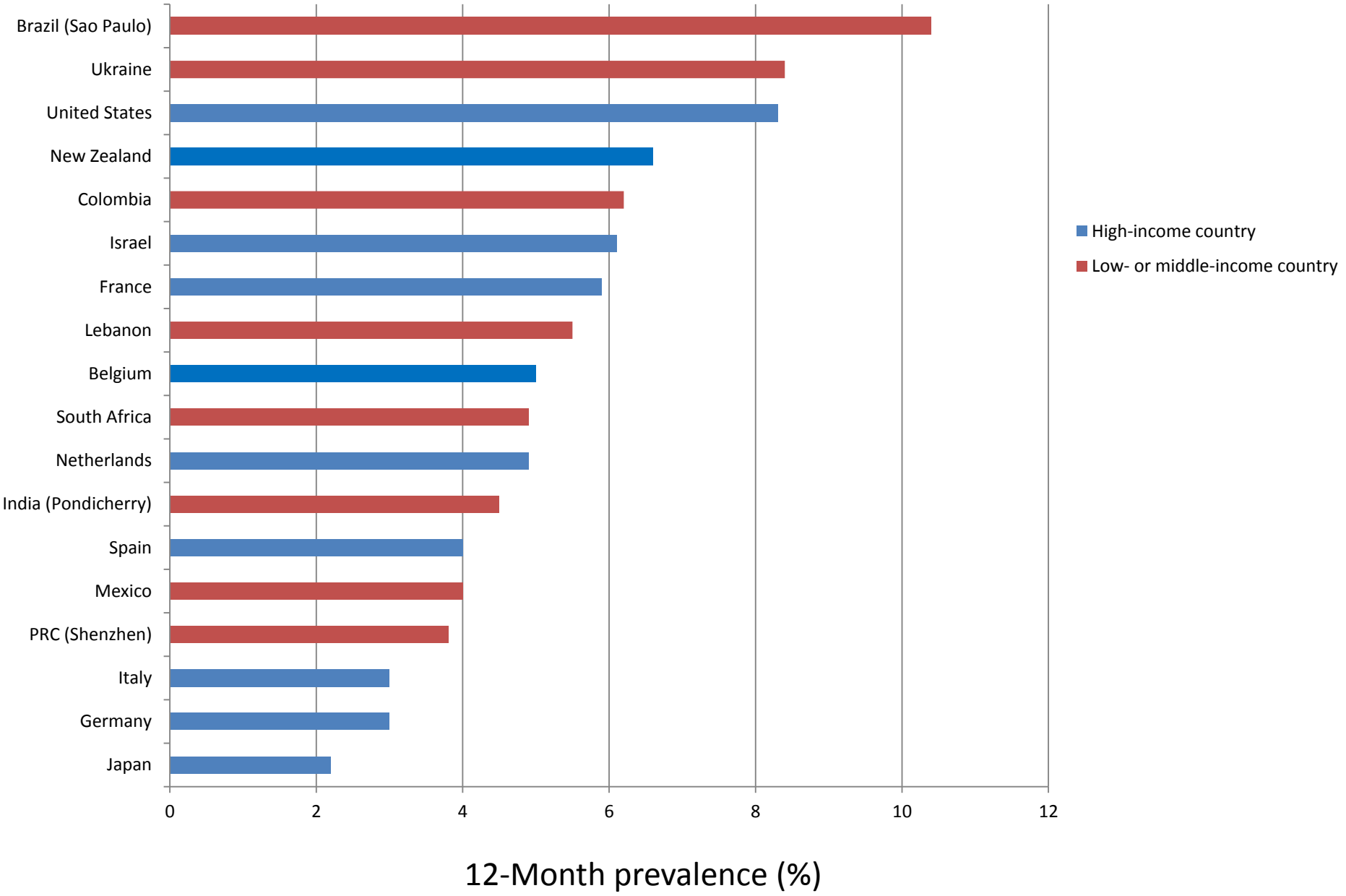
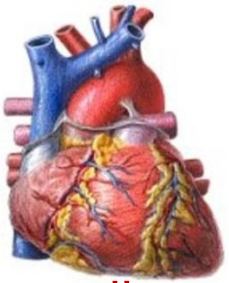

Brazil (Sao Paulo)
Ukraine
United States
New Zealand
Colombia
Israel
France
Lebanon
Belgium
South Africa
Netherlands
India (Pondicherry)
Spain
Mexico
PRC (Shenzhen)
Italy
Germany
Japan
0
2
4
6
8
10
12
High-income country
Low- or middle-income country
12-Month prevalence (%)

Figure 2

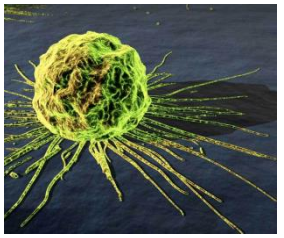
Mortality

RR=1.8



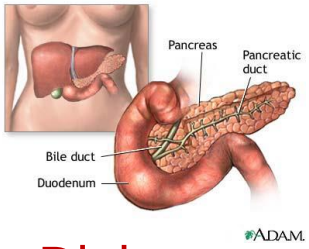
Heart disease

RR=1.8



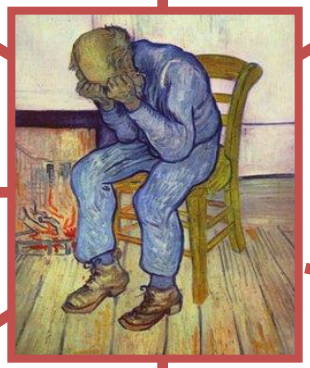
Cancer

RR=1.3



Diabetes

RR=1.6



RR=1.6

Obesity

RR=1.7

Disability

RR=1.8

Cognitive impairment

Figure 3

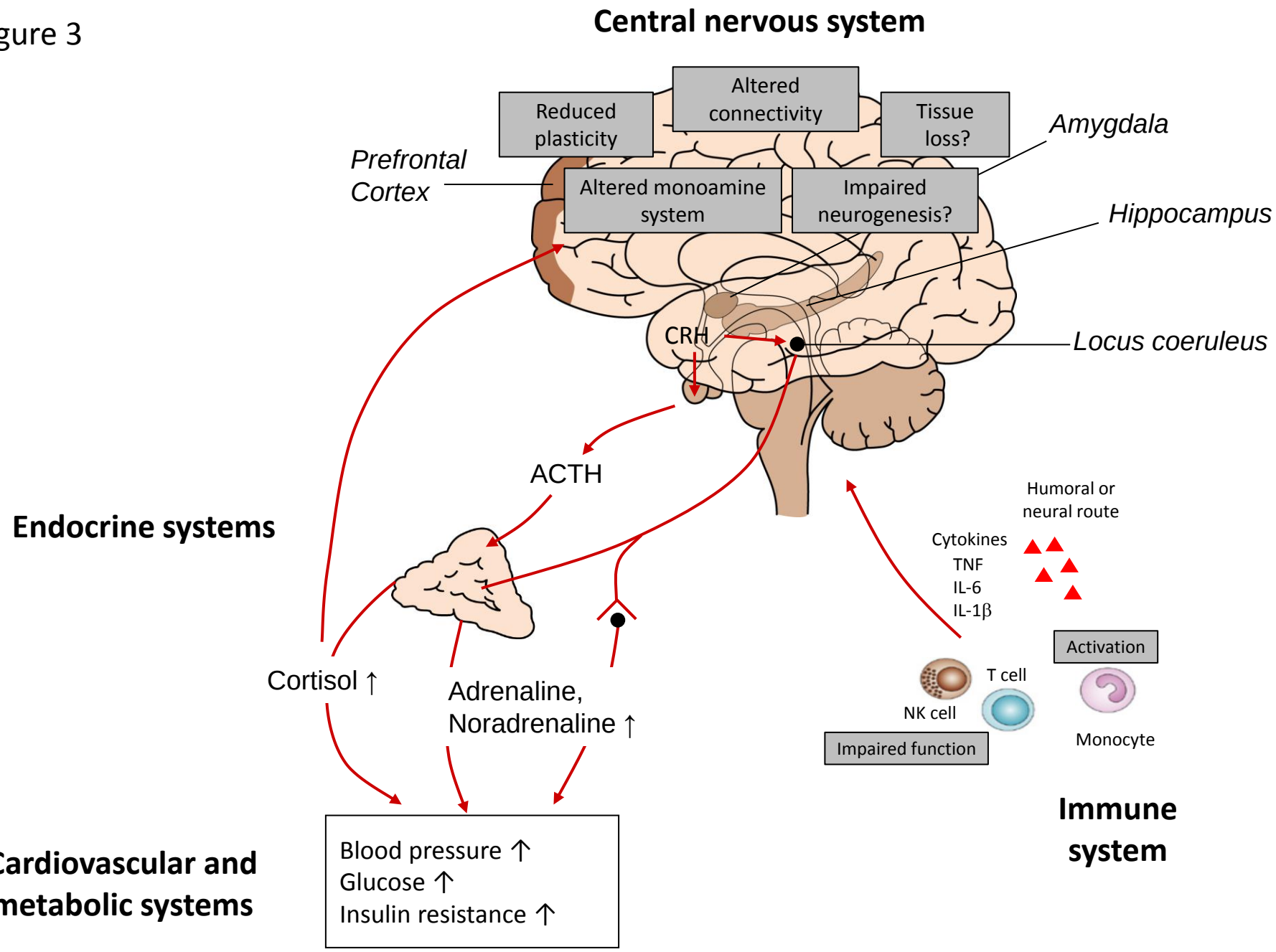

Central nervous system
Reduced plasticity
Altered connectivity
Tissue loss?
Amygdala
Prefrontal Cortex
Altered monoamine system
Impaired neurogenesis?
Hippocampus
CRH
Locus coeruleus
ACTH
Endocrine systems
Humoral or neural route
Cytokines
TNF
IL-6
IL-1β
Activation
T cell
NK cell
Monocyte
Impaired function
Immune system
Cortisol ↑
Adrenaline, Noradrenaline ↑
Blood pressure ↑
Glucose ↑
Insulin resistance ↑
Cardiovascular and metabolic systems

Figure 4

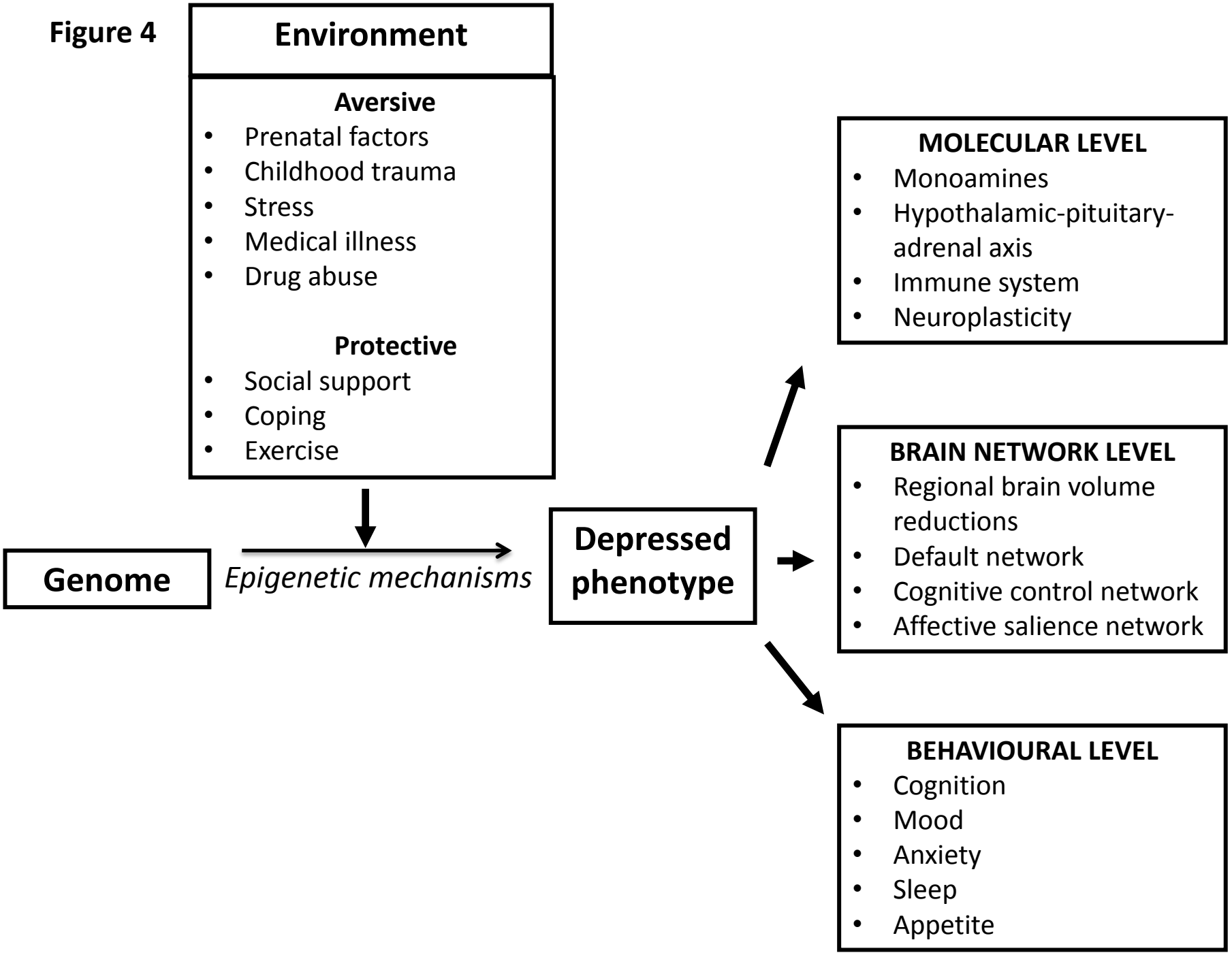

Environment
Aversive
Prenatal factors
Childhood trauma
Stress
Medical illness
Drug abuse
Protective
Social support
Coping
Exercise
Genome
Epigenetic mechanisms
Depressed phenotype
MOLECULAR LEVEL
Monoamines
Hypothalamic-pituitary-adrenal axis
Immune system
Neuroplasticity
BRAIN NETWORK LEVEL
Regional brain volume reductions
Default network
Cognitive control network
Affective salience network
BEHAVIOURAL LEVEL
Cognition
Mood
Anxiety
Sleep
Appetite

Figure 5

Data for Fig 5: Structural brain alterations in MDD			
Brain volumes [1]	**Effect size***	**95% CI (upper; lower)***	**Average volume difference to healthy controls***
Caudate [a]	**0.22**	**0.30; 0.06**	**-3,5%**
Putamen [a]	**0.25**	**0.43; 0.06**	**-4.1%**
Globus Pallidus [a]	**0.31**	**0.61; 0.02**	**-4.5%**
Thalamus	**0.34**	**0.60; 0.07**	**-6.7%**
Hippocampus [a,b]	**0.47**	**0.62; 0.32**	**-5.5%**
Frontal lobe	**0.29**	**0.53; 0.05**	**-3.8%**
Orbitofrontal cortex	**0.38**	**0.64; 0.11**	**-7.5%**
Gyrus rectus	**0.72**	**1.03; 0.41**	**-15.5%**

DRAFT FIGURE 5

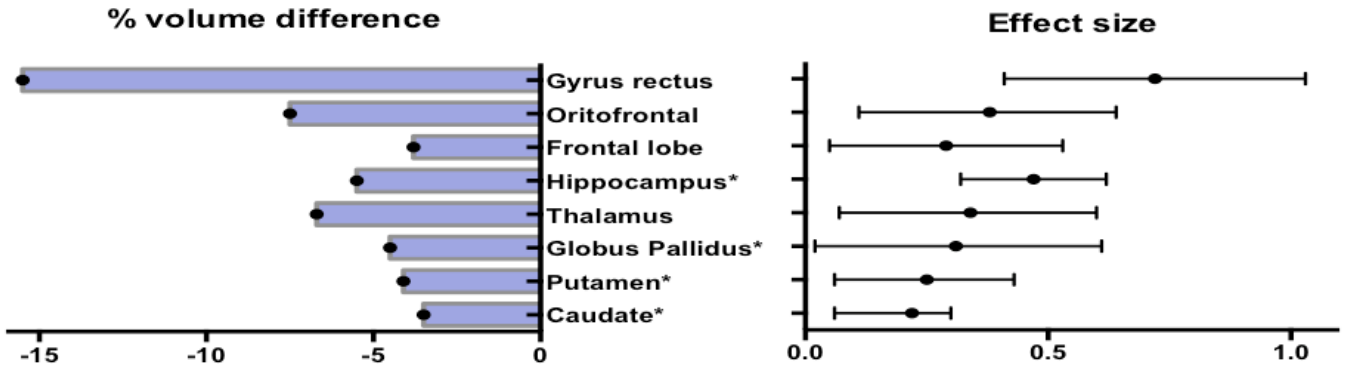
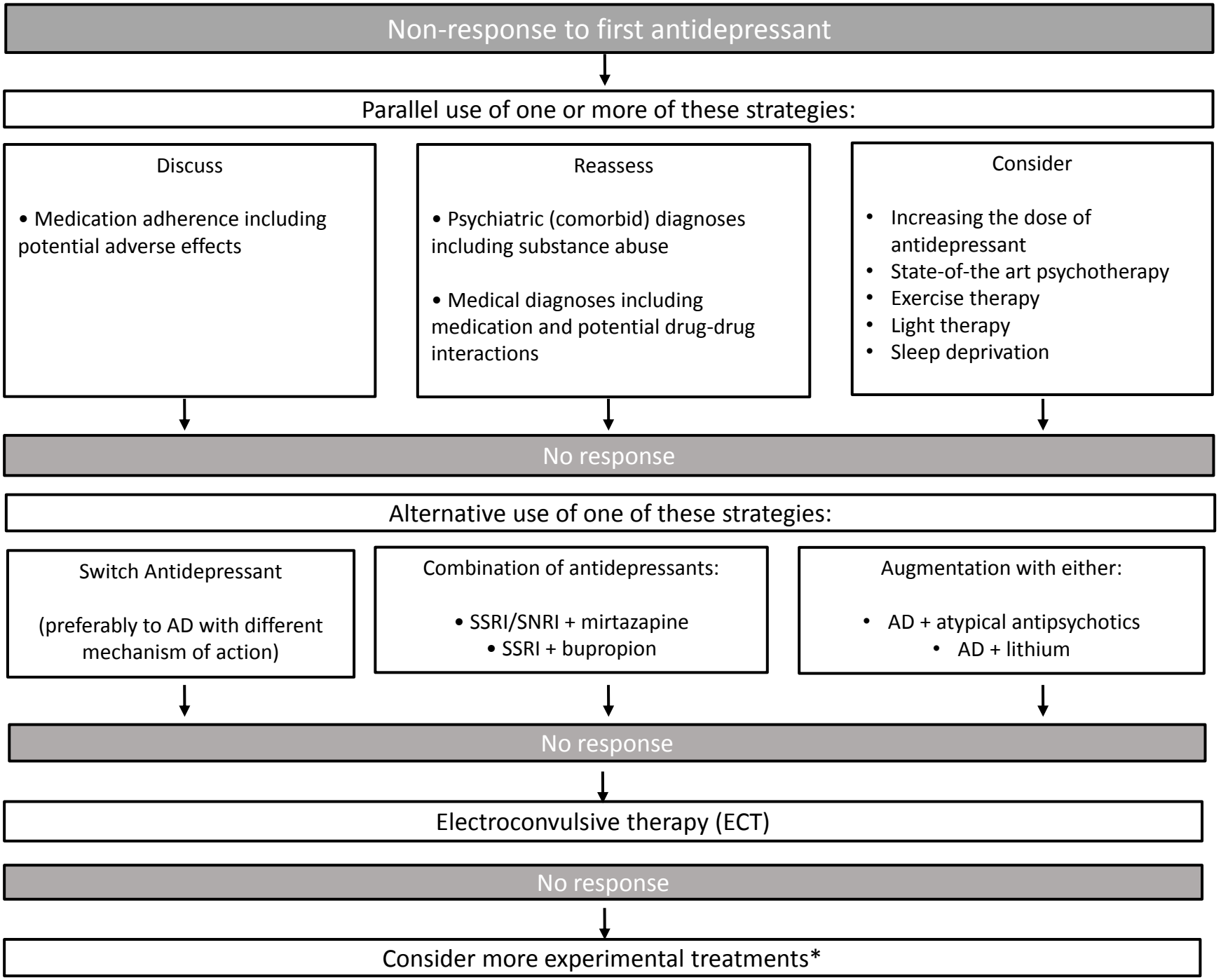


Figure 6


Non-response to first antidepressant
Parallel use of one or more of these strategies:
Discuss
• Medication adherence including potential adverse effects
Reassess
• Psychiatric (comorbid) diagnoses including substance abuse
• Medical diagnoses including medication and potential drug-drug interactions
Consider
• Increasing the dose of antidepressant
• State-of-the art psychotherapy
• Exercise therapy
• Light therapy
• Sleep deprivation
No response
Alternative use of one of these strategies:
Switch Antidepressant
(preferably to AD with different mechanism of action)
Combination of antidepressants:
• SSRI/SNRI + mirtazapine
• SSRI + bupropion
Augmentation with either:
• AD + atypical antipsychotics
• AD + lithium
No response
Electroconvulsive therapy (ECT)
No response
Consider more experimental treatments*