Major Depressive Disorder: Symptomatology, Diagnostic Validity, and Vulnerability-Stress Models with Implications for Prevention and Treatment

Albaraa Mesawi

University of South Carolina

ORCID: https://orcid.org/0009-0007-6371-9724

Author Note

Correspondence concerning this article should be addressed to Albaraa Mesawi at Albaraa010@gmail.com.

Abstract

Major Depressive Disorder (MDD) is a leading cause of disability, defined by Major Depressive Episodes (MDEs) comprising at least five of nine symptoms over two weeks with marked distress/impairment. This review outlines symptomatology and epidemiology (U.S. lifetime 15-17%; 12-month 6-7%; female:male ≈2:1; typical onset mid-20s). This review examines the categorical vs dimensional debate: taxometric evidence favors a continuum and supports hybrid practice (categorical decisions supplemented by dimensional severity). This review also critiques the DSM-5-TR on validity (no biomarkers; heterogeneity), reliability ($\kappa \approx .28$), thresholding, and bereavement-exclusion changes. A vulnerability-stress framework integrates psychological (hopelessness, negative schemas) and biological (5-HTTLPR × stress) diatheses with life events. Interventions include CBT ($g \approx .79$; relapse prevention), ACT (comparable to CBT), RO-DBT (short-term gains), exercise (moderate effects), and pharmacotherapy (SSRIs effective; SNRIs possibly superior in severe cases; ketamine rapid and sustained). Prevention reduces incidence (~22%); maintenance antidepressants roughly halve relapse risk. Personalized, integrated care is recommended.

Major Depressive Disorder (MDD) is the leading cause of disability globally as supported by epidemiological surveys that show MDD affects a reasonable number of people throughout their lifetime (Ferrari et al., 2013; Kessler et al., 2003). Understanding MDD requires an examination of its core diagnostic component, that is a Major Depressive Episode (MDE), which represents the distinct periods of symptoms that define the disorder (APA, 2022). This paper will provide a review of MDD, starting with its symptomatology, including the criteria for an MDE, and epidemiology, then discussing the categorical vs. dimensional classification debate, and providing an evaluation of the current DSM-5-TR diagnostic criteria for MDD. Lastly, there will be a review of psychological and biological vulnerability stress models of MDD's etiology, intervention and prevention.

Core Symptomatology & Epidemiology

The diagnosis of MDD hinges on the presence of one/more MDEs. An MDE is defined by a distinct period of significant depressive symptoms (APA, 2022). According to the DSM-5-TR (APA, 2022), an MDE involves experiencing at least five out of nine characteristic symptoms during the same two-week period that show a change from previous state of functioning. The diagnosis of MDD requires that a person has met the criteria for at least one MDE (APA, 2022). The symptom list is: depressed mood, anhedonia (e.g., reduced libido), change in appetite, insomnia, psychomotor agitation/retardation, fatigue/energy loss, worthlessness, reduced cognitive ability (e.g., concentration) or indecisiveness, thoughts of death and (attempting)

suicide. To meet the criteria for an MDE, either depressed mood or anhedonia must be present in most activities (for at least two weeks). These symptoms must cause major distress/impairment in daily functioning (e.g., occupational, social, etc.), and they must not be explained by substance use, medical condition, or another mental disorder (e.g., schizoaffective disorder) (APA, 2022). As for the prevalence of MDD, 15-17% of the U.S. population have been diagnosed with MDD in their lifetime, and the 12-month prevalence rate is ~6-7% according to the National Comorbidity Survey (Kessler et al., 2003); the 12-month prevalence of MDD in young adults is 7% according to the APA (2022). Similarly, cross-national epidemiological research by the World Health Organization finds that lifetime rate of MDD to be about 12-15% in high income countries and somewhat lower (~11%) in low to middle income countries, with the exact rates varying from country to country; rates of MDD over one year varied across the range from 2-6% in Asian countries compared to 5% in Western nations (Bromet et al., 2011).

According to Kleinman (2004), the core symptoms (i.e., anhedonia and depressed mood) of MDD could be observed across cultures with known variations in the expression and perception of distress. Recognition and diagnosis can be affected if, in some cultures, the emphasis is on somatic (e.g., fatigue, sleep problems, etc.) rather than emotional (e.g., sadness) symptoms. For example, Chinese individuals have more somatic complaints and seldom depressed mood or have feelings of worthlessness than Western patients, representing a cultural tendency to somatize emotional distress (Parker et al., 2001). However, such differences mean that standard DSM criteria may underdiagnose depression in cultural groups who express their depression through physical symptoms. Additionally, women are on average about twice as likely as men to have MDD and this sex difference has been consistently observed across diverse cultures and

studies (Bromet et al., 2011; Albert, 2015). A female-to-male ratio of 2:1 occurs in adolescence and continues into adulthood, which has been attributed to a complex interplay of biological (hormonal), psychosocial, and cultural factors (Albert, 2015). Although MDD can occur at any age, and there are some data suggesting slightly earlier onset for men compared to women, the average age of onset is most commonly in the mid-20s, and early onset in adolescent or early adulthood is a common pattern of onset (Bromet et al., 2011). The course of the illness is variable; some people are depressed on only one occasion that passes, while others are depressed often. Sociodemographic factors also influence risk in addition to sex, factors like socioeconomic status, unemployment, divorced or separated also confer greater risk for depression (Bromet et al., 2011).

Classification Debate: Dimensional or Categorical?

Traditional psychiatric classification such as that in the DSM system classifies MDD as a categorical, binary diagnosis where either one has it or not. A categorical system can be clinically useful due to the dichotomous nature of the diagnosis which can inform clinicians whether to treat, qualify for services, or include in research. To be diagnosed with such disorder in the DSM, one must meet the specific cut-off criteria (a threshold number of symptoms, duration, and impairment (APA, 2022). Categorical systems assume that MDD is qualitatively different from normal mood variation, and that there is a distinction between disorder and order that defines the presence of MDD. The categorical view is consistent with how clinicians often have to act/proceed and is simple. However, research demonstrates that depressive symptoms spread continuously through the population because there exists no clear threshold defining normal versus ill states. Empirical evidence obtained via taxometric analyses show that

depression exists as a latent dimensional construct according to studies done by Ruscio & Ruscio (2000) and Hankin et al. (2005). Ruscio and Ruscio (2000) analyzed depression symptom data which supported a dimensional model over alternatives showing that increased symptoms produce higher levels in a single underlying continuum rather than normal-disordered state categorization. The results of a taxometric evaluation on a large youth sample revealed that depressive symptoms extended continuously from non-depressed to depressed ranges without identifying any clear cutoff between groups (Hankin et al., 2005). Additionally, depression severity increases gradually from those with four depressive symptoms up to those with five symptoms of depression since their average impairment differences remain minimal (Karsten et al., 2010). Karsten et al. (2010) findings indicate that subclinical depression symptoms differ from full criteria depression mostly through intensity instead of distinct class distinctions.

Criticism of DSM-5 Diagnostic Criteria

As time went on, dissatisfaction with rigid categories has risen, and shifts to reformulation of mental diseases have begun. A major example is the National Institute of Mental Health's Research Domain Criteria (RDoC) project, which positions itself from the start as an enterprise toward a paradigm change to dimensional framework for understanding psychopathology (Insel et al., 2010). RDoC aims to characterize mental disorders (including depression) based on behavioral dimensions and neurobiological measures (continuous measures of negative affect, cognitive functioning, anhedonia, etc.), instead of the traditional diagnostic categories (Insel et al., 2010). Another somewhat recent example of the dimensional view is the Hierarchical Taxonomy of Psychopathology (HiTOP) that proposes a spectrum model with disorders of depression, for example, embedded in wider spectra and continuous traits which also represent

the similarities between disorders and symptom gradations (Kotov et al., 2017). Both developments mirror a trend in a broader paradigm shift of psychiatry towards dimensional models of studying mental disorders (like MDD) because diagnostic categories described by DSM and ICD are the established standards for clinical practice.

Moreover, research findings suggest that dimensional evaluation of symptoms and their intensity levels deliver better outcome predictions and therapeutic guidance than categorical diagnosis systems (Fried & Nesse, 2015). Clinicians treating MDD patients usually find that dimensional assessments deliver valuable information about symptom severity, which standard present/absent diagnostic systems exclude (Fried & Nesse, 2015). DSM-5-TR added severity specifiers to MDD diagnosis (i.e., mild, moderate, severe) and recommended standardized rating scales for additional diagnostic assessment (APA, 2022). Studies confirm that low levels of depression symptoms exist across the general population and such mild symptoms can elevate the risk of developing future disorders. The usage of dimensional methods creates problems in practical settings because healthcare providers need definitive decision boundaries for evaluating clinical situations (e.g., starting medication). The hybrid diagnostic approach which maintains categorical conditions for clinical use also incorporates multidimensional symptom measurement methods for identifying key characteristics and vulnerabilities (Fried & Nesse, 2015), and this aligns with the continuum nature of depressive experiences (Insel et al., 2010; Hankin et al., 2005).

Another criticism of MDD diagnosis based on the DSM involves its ability to represent an isolated medical condition. To achieve validity in psychiatric diagnosis a diagnostic category

needs to represent a natural disease which has unique pathophysiological foundations or a meaningful disease progression. Medical experts have not identified any distinct biomarkers for MDD diagnosis and the disease's origin pathways show extensive diversity which raises doubts about the DSM's ability to represent a single disorder in nature (Insel et al., 2010). Researchers behind DSM-5 suggested that new discoveries in neuroscience and genetics would strengthen criteria validity for MDD by establishing biological markers (Lieblich et al., 2015). The diagnosis of MDD still depends on symptom counts and clinical judgment because biomarkers have not been included in the diagnostic criteria. The guidelines in DSM-5-TR for MDD diagnosis potentially allow too many diverse conditions to meet criteria thus potentially including cases with essential differences. Two depressive episodes meeting MDD criteria could stem from different origins even though both fulfill the diagnostic requirements; for example, one might begin after marital separation and another might appear during the teenage years. The wide spectrum of cases included under this category threatens to compromise the conceptual validity, which is the belief that MDD patients share a common medical condition according to Wakefield (2013). A key problem exists regarding the diagnostic reliability because clinicians struggle to maintain uniformity when they apply diagnostic criteria. The diagnosis of MDD loses its usefulness since clinicians cannot identify patients correctly when reliability between clinicians fails to meet standards. Interrater reliability tests for DSM-5 revealed MDD received 'questionable' agreement beyond chance through a kappa statistic of .28 according to Regier et al. (2013). The diagnostic agreement between psychiatrists when assessing patients for MDD reaches only moderate levels despite the extensive occurrence of MDD (Regier et al., 2013). The subjective evaluation of symptoms, including 'markedly diminished interest' and 'excessive

guilt,' is difficult to assess and helps explain the low reliability, especially when symptom reports are influenced by comorbid conditions and cultural differences.

Moreover, some researchers questioned the use of five symptoms as a diagnostic requirement because a person with four severe symptoms could experience equivalent impairment but would not get diagnosed (Fried & Nesse, 2015). The precise accuracy of DSM diagnostic thresholds becomes questionable with this observation. DSM-5 criteria have also created a heterogeneous group of patients under the single diagnosis label of MDD. Because two individuals with MDD could share a single symptom, or share none at all in that one has depressed mood and four other symptoms and the other has anhedonia and four other symptoms (Fried & Nesse, 2015). The variability complicates treatment because different symptom alignments may respond to different interventions, and it dilutes the findings of research studies, because clinical trials for MDD may be enrolling biologically/psychologically diverse cases. Some researchers instead argue that future diagnostic refinements should subtype depression more narrowly (Fried & Nesse, 2015) (e.g., melancholic subtype or an atypical subtype, etc.) or use symptom dimensions such as separate ratings for anxious distress, melancholia (etc.) to create more homogeneous groups.

Moreover, the criteria's overlap with normal human experiences and other disorders have also been criticised. For example, eliminating the bereavement exclusion, permitting a diagnosis of MDD within early weeks after the passing away of a loved one if the individual satisfies the symptom criteria (APA, 2022). Some critics of this change argue that it blurs the line between normal grieving and clinical depression, even defining healthy and expectable reactions to losses as a mental disorder (Wakefield, 2013). Notably, Wakefield (2013) argued that by removing the

bereavement exclusion, the concept validity of MDD is undermined because ‘disorder’ is not sufficiently differentiated from ‘intense but normal sorrow.’ Thus resulting in over diagnosis and unnecessary treatment (prescribing antidepressants - will be discussed more later) of individuals who would likely recover naturally and with social support and time (i.e., protective factors) (Kavan & Barone, 2014). However, proponents for the DSM-5 change claimed that grief related depression can be severe and clinical and that there was no scientific bases for exempting only one kind of life stress (e.g., bereavement) from counting toward MDD while other similar stress-induced depressions (e.g., after job loss/divorce) count as MDD (Pies, 2014). In support of the removal, a study by Kendler et al. (2008) showed that bereavement related depression (meeting full MDD criteria) did not differ in clinical indicators (e.g., symptom profile, duration, and family history of depression) from depressive episodes triggered by other stressful events. The exclusion of cases based solely on cause (bereavement) could lead to missing individuals who need clinical intervention/attention. The DSM-5-TR provides guidance to practitioners about assessing loss context while distinguishing MDD from grief since grief primarily manifests as waves of emptiness and loss which differ from MDD symptoms of persistent depressed mood and self-critical thoughts (APA, 2022). Overall, this controversy underscores the importance of clinical judgement; clinicians are urged to carefully evaluate the nature of symptoms, cultural context, and the patient’s functional impairment before deciding that MDD is present (Pies, 2014).

Vulnerability-Stress Models, Intervention & Prevention of MDD

The understanding of MDD as being caused from interplay of underlying vulnerabilities (diathesis) and precipitating stressors. According to Zubin and Spring (1977), the emergence of

psychopathology requires less environmental stress when three factors exist simultaneously: genetic neurodevelopmental abnormalities, disrupted attachments that lead to maladaptive cognitive systems, and deficits of executive functioning. Essentially, greater vulnerability leads to decreased stress threshold which causes the emergence of psychopathology. Monroe & Simons (1991) updated the diathesis-stress model via their differentiation of fixed from changing vulnerability factors. Negative schemas and neurobiological dysregulation such as serotonin depletion together with genes and early childhood adversities constitute stable vulnerabilities. Dynamic vulnerabilities include cognitive response patterns and sleep disturbances that are considered as transient vulnerabilities along with neurochemical sensitivity to stress.

This section reviews two of the most well-defined vulnerability stress models of MDD, psychological and biological. Starting with the psychological model is the cognitive vulnerability theory of depression as reflected by the hopelessness theory (Abramson et al., 1989). This model states that some cognitive styles become vulnerabilities because they predispose a person to depression if a major stressful life event occurs. People who exhibit a depressogenic attributional style tend to develop hopelessness after encountering negative events because they interpret these events as permanent and widespread. A person with this cognitive style would say ‘ I did badly on this presentation because I am incompetent (internal cause), and no matter how much I prepare, I will never get better at it (global, stable inference).’ According to the theory, if people with these negative cognitive schemas undergo a major stressor or a series of stressors (e.g., a significant loss, rejection, and failure), it is likely they will experience hopelessness, which acts as a proximal sufficient cause of depressive episode marked by symptoms such as apathy, sadness, and suicidality (Abramson et al., 1989). The hopelessness model expanded prior

frameworks (e.g., Beck and Seligman) by explicitly proposing hopelessness depression as a subtype of depression caused by the triggering event (Abramson et al., 1989).

Moreover, the cognitive vulnerability stress hypothesis has generally been supported in empirical tests. Alloy et al. (2000) assessed adolescents and young adults with high-risk, and with low risk cognitive styles over time. Consistent with the diathesis stress prediction, they found that the high risk (negative cognitive style) group had statistically significant higher lifetime incidence of major depressive episodes and of hopelessness depression than the low risk group, especially following stressful stimulus (Alloy et al., 2000). This indicates that depression can be precipitated by the activation of these and other cognitive vulnerabilities (e.g., negative schemas) typically associated with depression when adversity strikes. As with the other psychological vulnerabilities (e.g., tendency to ruminate or insecure attachment styles) that have been shown to interact with stress in predicting depressive onset, these cognitive personality factors significantly shape the reactivity of stress in MDD pathogenesis (Hankin et al., 2005). Psychological vulnerability-stress model stresses the importance of mind and environment: that adverse events are not the cause of depression, but it is how the events are *perceived* in a person's mind, which is influenced by pre-existing cognitive schemas.

Researchers have applied biological diathesis stress models to clarify why some individuals face depression when stressed yet others remain seemingly unaffected by stress. The serotonin transporter gene (5-HTT) interaction with stressful life events serves as an important demonstration of the GxE relationship. Caspi et al. (2003) used their research to show that variation in the 5-HTTLPR gene located at the 5-HTT promoter controls how life stress affects

the risk for developing depression. Research based on a longitudinal birth cohort analysis determined that people with one or two short variants of 5-HTTLPR showed elevated chances of developing depression from stressful stimuli when compared to people with two long variants (Caspi et al., 2003). Depression outcomes were predicted by the biological vulnerability (malfunctioning serotonin transporter efficiency genes) interacting with environmental stress factors (Caspi et al., 2003). Individuals who possess extensive biological vulnerabilities related to mood disorders, accompanied by predisposing temperament variations (e.g., neuroticism), are usually at high risk for developing depression following stress exposure. An individual at higher risk (e.g., possessing genetic or neurochemical vulnerability) for MDD will likely develop the condition after adverse life events activate their predispositions. Another person with those same circumstances but who maintains positive self-esteem and an optimistic perspective (with protective factors) tends to remain healthy in safe environments until they experience major stressors, and is likely to bounce back to baseline. The vulnerability stress framework helps us understand how depression develops from multiple key components but different stressful events do not result in depression in everyone (multifinality).

The biological and psychological models have several implications on interventions and preventions. In this section, I will discuss psychotherapy, physical, and pharmacological interventions and preventions. A meta-analysis of 409 trials shows that CBT achieves substantial symptom reduction effects (Hedges' $g \approx .79$) which surpasses control conditions (Cuijpers et al., 2023). New clinical tests show that CBT produces similar health results to antidepressants while providing research on how CBT maintains effectiveness over time which leads to fewer depressive relapses (Cuijpers et al., 2023; Cuijpers et al., 2008), Moreover, results from

evaluations show that third wave ACT therapy matches the success rates of traditional CBT approaches. Research conducted through meta-analytic reviews show there is moderate symptom reduction in depression using ACT than standard care, and ACT delivers comparable results to CBT regarding the effectiveness of treatment (A-Tjak et al., 2015). Although the origin of DBT was created to treat BPD, Radically Open DBT (for people with refractory depression with emotional overcontrol association) demonstrated significant short-term improvements in depressive symptoms at seven months in a randomized trial but effects did not reach statistical significance at follow-ups (Lynch et al., 2018)[1]. Additionally, research shows that walking (e.g., aerobic exercises) and practicing similar exercise programs at moderate intensity result in moderate depression symptom reduction (MDD included) in comparison with control groups (Schuch et al., 2016); similar results were observed for adolescents based on a meta-analysis (Carter et al., 2016). As for pharmacological approaches to treating MDD, SSRIs (e.g., fluoxetine and sertraline) are effective because they block serotonin reuptake and increase serotonin in synapses. A meta-analysis by Cipriani et al. (2018) found that SSRIs were statistically significant in terms of effectiveness compared to placebo in its treatment of acute MDD in adults. Research on SNRIs shows that they can provide more benefit than SSRIs for severe depression treatment due to their dual mechanism on serotonin and norepinephrine reuptake (Lambert & Bourin, 2002); SNRIs may be more effective than SSRIs in reducing depression generally (Moret & Briley, 2011). Tricyclic antidepressants are an option but the side effects cause withdrawal compared to SSRIs which shows intolerance in patients (MacGillivray et al., 2003). A study by Alnefeesi et al. (2022) found that rapid antidepressant effects can emerge in hours after administration of sub-anesthetic ketamine which is mainly mediated via NMDA receptor antagonism and downstream synaptogenesis signaling pathways. These effects

[1] Though its long-term efficacy and cost-effectiveness are limited.

can be sustained with repeated doses (including intranasal esketamine) and there is evidence supporting that antidepressant benefits extend from mid- to long-term treatment without loss of efficacy (Alnefeesi et al., 2022).

Psychological based preventive interventions using CBT or interpersonal therapy have reduced the incidence of new depressive episodes in high risk populations by about 22% (Cuijpers et al., 2008). Such programs given in schools or in primary care settings teach coping and problem solving skills that may delay or prevent MDD from emerging. Individuals in remission who continue their treatment experience lower chances of depression returning. Studies performed as meta-analyses in maintenance antidepressant trials show that patients who stay on medication experience a near 50% decrease in relapse risk (Hansen et al., 2008). Overall, prevention depends on the kind of client/patient; some prefer medication interventions, and some prefer psychologically based interventions.

In conclusion, research shows that MDD functions as a medically complicated disorder which develops from biological and psychological factors that converge with environmental triggers. This review also highlighted that the diagnosis of MDD is established through the occurrence of one/more MDEs, defined by specific symptom criteria in the DSM (APA, 2022). Clinical diagnostics based on categories and dimensions serve as useful tools to make treatment decisions. Research shows that psychotherapies' (e.g., CBT, DBT, ACT, etc.) effectiveness and pharmacological medication use (e.g., SSRIs, SNRIs, TCAs, ketamine, etc.) and prevention methods require a personalized integrated treatment plan (Bromet et al., 2011; Caspi et al., 2003; Cuijpers et al., 2008).

References

Abramson, L. Y., Metalsky, G. I., & Alloy, L. B. (1989). Hopelessness depression: A theory‐based subtype of depression. *Psychological Review, 96*(2), 358–372.

A-Tjak, J. G. L., Davis, M. L., Morina, N., Powers, M. B., Smits, J. A. J., & Emmelkamp, P. M. G. (2015). A meta-analysis of the efficacy of acceptance and commitment therapy for clinically relevant mental and physical health problems. *Psychotherapy and Psychosomatics, 84*(1), 30–36.

Albert, P. R. (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience, 40*(4), 219–221.

Alloy, L. B., Abramson, L. Y., Hogan, M. E., Whitehouse, W. G., Rose, D. T., Robinson, M. S., … Lapkin, J. B. (2000). The Temple‐Wisconsin Cognitive Vulnerability to Depression Project: Lifetime history of Axis I psychopathology in individuals at high and low cognitive risk for depression. *Journal of Abnormal Psychology, 109*(3), 403–418.

Alnefeesi, Y., Chen‐Li, D., Krane, E., Jawad, M. Y., Rodrigues, N. B., Ceban, F., Di Vincenzo, J. D., Meshkat, S., Ho, R. C. M., Gill, H., Teopiz, K. M., Cao, B., Lee, Y., McIntyre, R. S.,

& Rosenblat, J. D. (2022). Real‐world effectiveness of ketamine in treatment‐resistant depression: A systematic review & meta‐analysis. *Journal of Psychiatric Research, 151*, 693–709. https://doi.org/10.1016/j.jpsychires.2022.04.037

American Psychiatric Association. (2022). *Diagnostic and Statistical Manual of Mental Disorders (5th ed., text rev.)*.

Bromet, E. J., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., … Kessler, R. C. (2011). Cross‐national epidemiology of DSM‐IV major depressive episode. *BMC Medicine, 9*(1), 90.

Carter, T., Morres, I. D., Meade, O., & Callaghan, P. (2016). The effect of exercise on depressive symptoms in adolescents: A systematic review and meta‐analysis. *Journal of the American Academy of Child & Adolescent Psychiatry, 55*(7), 580–590.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., … Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386–389.

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., … & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet, 391*(10128), 1357–1366.

Cuijpers, P., van Straten, A., Smit, F., Mihalopoulos, C., & Beekman, A. F. T. (2008). Preventing the onset of depressive disorders: A meta-analytic review of psychological interventions. *American Journal of Psychiatry, 165*(10), 1272–1280.

Cuijpers, P., Miguel, C., Harrer, M., Plessen, C. Y., Ciharova, M., Ebert, D., & Baumeister, H. (2023). Cognitive behavior therapy vs. control conditions, other psychotherapies, pharmacotherapies and combined treatment for depression: A comprehensive meta-analysis of 409 trials. *World Psychiatry, 22*(1), 105–115.

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., … Whiteford, H. A. (2013). Burden of depressive disorders by country, sex, age, and year: Findings from the Global Burden of Disease Study 2010. *PLoS Medicine, 10*(11), e1001547.

Fried, E. I., & Nesse, R. M. (2015). Depression is not a consistent syndrome: An investigation of unique symptom patterns in the STAR*D study. *Journal of Affective Disorders, 172*, 96–102.

Hankin, B. L., Fraley, R. C., Lahey, B. B., & Waldman, I. D. (2005). Is depression best viewed as a continuum or discrete category? A taxometric analysis of childhood and adolescent depression in a population‐based sample. *Journal of Abnormal Psychology, 114*(1), 96–110.

Hansen, R. A., Gartlehner, G., Lohr, K. N., Gaynes, B. N., & Carey, T. S. (2008). Meta-analysis of major depressive disorder relapse and recurrence with second generation antidepressants. *Psychiatric Services, 59*(10), 1121–1130.

Insel, T. R., Cuthbert, B. N., Garvey, M. A., Heinssen, R. K., Pine, D. S., Quinn, K. J., Sanislow, C. A., & Wang, P. S. (2010). Research domain criteria (RDoC): Toward a new

classification framework for research on mental disorders. *American Journal of Psychiatry, 167*(7), 748–751.

Karsten, J., Hartman, C. A., Ormel, J., Nolen, W. A., & Penninx, B. W. (2010). Subthreshold depression based on functional impairment better defined by symptom severity than by number of DSM‐IV symptoms. *Journal of Affective Disorders, 123*(1–3), 230–237. https://doi.org/10.1016/j.jad.2009.10.013

Kavan, M. G., & Barone, E. J. (2014). Grief and major depression—Controversy over changes in DSM-5 diagnostic criteria. *American Family Physician, 90*(10), 690–694.

Kendler, K. S., Myers, J., & Zisook, S. (2008). Does bereavement‐related major depression differ from major depression associated with other stressful life events? *American Journal of Psychiatry, 165*(11), 1449–1455.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., … Wang, P. S. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS‐R). *Journal of the American Medical Association, 289*(23), 3095–3105.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Bagby, R. M., Brown, T. A., … Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A Dimensional Alternative to Traditional Nosologies. *Journal of Abnormal Psychology, 126*(4), 454–477. https://doi.org/10.1037/abn0000258

Kleinman, A. (2004). Culture and depression. *New England Journal of Medicine, 351*(10), 951–953.

Lambert, O., & Bourin, M. (2002). SNRIs: Mechanism of action and clinical features. *Expert Review of Neurotherapeutics, 2*(6), 849–858.

Lieblich, S. M., Castle, D. J., Pantelis, C., Hopwood, M., Young, A. H., & Everall, I. P. (2015). High heterogeneity and low reliability in the diagnosis of major depression will impair the development of new drugs. *BJPsych Open, 1*(2), e5–e7.

Lynch, T. R., Hempel, R. J., Whalley, B., Byford, S., Chamba, R., Clarke, P., Clarke, S., Kingdon, D., O'Mahen, H., Remington, B., Rushbrook, S. C., Shearer, J., Stanton, M., Swales, M., Watkins, A., & Russell, I. T. (2018). Radically open dialectical behaviour therapy for refractory depression: The RefraMED RCT. *Efficacy and Mechanism Evaluation, 5*(7). https://doi.org/10.3310/eme05070

MacGillivray, S., Arroll, B., Hatcher, S., Ogston, S., Reid, I., Sullivan, F., … & Williams, B. (2003). Efficacy and tolerability of SSRIs compared with tricyclic antidepressants in primary care: A meta-analysis. *BMJ, 326*(7397), 1014.

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin, 110*(3), 406–425.

Moret, C., & Briley, M. (2011). The importance of norepinephrine in depression. *Neuropsychiatric Disease and Treatment, 7*(Suppl 1), 9–13. https://doi.org/10.2147/NDT.S19619

Parker, G., Cheah, Y. C., & Roy, K. (2001). Do the Chinese somatize depression? A cross‐cultural study. *Social Psychiatry and Psychiatric Epidemiology, 36*(6), 287–293.

Pies, R. (2014). The bereavement exclusion and DSM‐5: An update and commentary. *Innovations in Clinical Neuroscience, 11*(7–8), 19–22.

Regier, D. A., Narrow, W. E., Clarke, D. E., Kraemer, H. C., Kuramoto, S. J., Kuhl, E. A., & Kupfer, D. J. (2013). DSM‐5 field trials in the United States and Canada, Part II: Test–retest reliability of selected categorical diagnoses. *American Journal of Psychiatry, 170*(1), 59–70.

Ruscio, J., & Ruscio, A. M. (2000). Informing the continuity controversy: A taxometric analysis of depression. *Journal of Abnormal Psychology, 109*(3), 473–487.

Schuch, F. B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P. B., Silva, E. S., … & Stubbs, B. (2016). Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *Journal of Psychiatric Research, 77*, 42–51.

Wakefield, J. C. (2013). The DSM‐5 debate over the bereavement exclusion: Psychiatric diagnosis and the future of empirically supported treatment. *Clinical Psychology Review, 33*(7), 825–845.

Zubin, J., & Spring, B. (1977). Vulnerability: A new view of schizophrenia. *Journal of Abnormal Psychology, 86*(2), 103–126.