NIH Public Access
Author Manuscript
Curr Psychiatry Rep. Author manuscript; available in PMC 2014 September 01.

Published in final edited form as:
Curr Psychiatry Rep. 2013 September ; 15(9): 386. doi:10.1007/s11920-013-0386-z.

Is Depression Simply a Nonspecific Response to Brain Injury?

Stephen M. Strakowski, MD, **Caleb M. Adler, MD**, and **Melissa P. DelBello, MD**
Division of Bipolar Disorders Research, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati OH

Abstract

Depressive disorders are among the most common ailments affecting humankind and some of the world's leading causes of medical disability. Despite being common, disabling and a major public health problem, the etiology of depression is unknown. Indeed, investigators have suggested that the causes of depression are multiple and multi-factorial. With these considerations in mind, in this article we examine the hypothesis that our inability to identify the causes of depressive disorders is because depression is a nonspecific epiphenomenon of brain injury or insult arising through multiple pathways.

Keywords

Depression; Depressive symptoms; Comorbid psychiatric disorders; Comorbid neurological and medical disorders; Neurobiology of depression; Brain injury; Risk factors; Treatment; Mood disorders; Psychiatry

Introduction

Depressive disorders are among the most common ailments affecting humankind. Approximately 7% of the population experiences major depression annually (e.g., 13-14 million Americans) and the lifetime risk is 17% (1). Major depression is one of the world's leading causes of medical disability, if not the leading cause (2). Major depression occurs commonly throughout the lifespan, although it is more common in women than men. Poverty and low socioeconomic status increase the risk of depression, as do multiple other medical, neurological and psychiatric conditions. Despite being common, disabling and a major public health problem, the etiology of depression is unknown; multiple studies inconclusively define the neurobiological or genetic basis of the condition. Indeed, investigators have suggested that the causes of depression are multiple and multi-factorial. With these considerations in mind, in this article we examine the hypothesis that our

Please address communications to: Stephen M. Strakowski, MD, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati COM, 260 Stetson Suite 3200, Cincinnati, OH 45267-0559. Telephone: 513-558-4274. Fax: 513-558-0187. Stephen.Strakowski@uc.edu..

Compliance with Ethics Guidelines

Conflict of Interest

Stephen M. Strakowski serves as chair of two data and safety monitoring boards for Sunovion.
Caleb M. Adler
Melissa P. DelBello has received research support from AstraZeneca, Amylin, Eli Lilly, Pfizer, Otsuka, GlaxoSmithKline, Merck, Martek, Novartis, Lundbeck, and Shire; has served on speakers bureaus for Otsuka, Merck, and Bristol-Myers Squibb; and has received honoraria and travel support for serving as a consultant/advisory board member for Merck, Pfizer, Dey, Lundbeck, Sunovion, and Otsuka.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

inability to identify the causes of depressive disorders is because depression is a nonspecific consequence of brain injury or insult arising through multiple pathways. Importantly, this article is not intended to be an exhaustive review of any of the areas discussed, but instead is (hopefully) a thoughtful opinion paper to challenge our thinking about this common condition.

Depression criteria are relatively nonspecific

The DSM-5 criteria for major depression are listed in Table 1; criteria in other diagnostic systems (e.g. ICD-10) are similar (3,4). 'Minor' depression and dysthymia share many of the same symptoms, albeit to a lesser degree and with varying temporal requirements. For all of these conditions, there is no single definitive symptom or objective marker of the diagnosis, similar to other psychiatric conditions. Consequently depressive disorders are defined by combinations of symptoms that commonly co-occur (i.e., syndromes) and provide some utility for establishing evidence-based treatment guidelines. The symptoms that define depression are, in and of themselves, relatively nonspecific. They include changes in sleep, appetite and energy that can be increased or decreased; negative mood states that include sadness, generalized dysphoria, anxiety, and irritability (in teens); and self-esteem assessments (e.g. worthlessness, excessive guilt) that may reflect a multitude of circumstances and are difficult to quantify. Perhaps the most specific symptom is anhedonia, although it too arises from a variety of neuropsychiatric and medical conditions. Factors underlying suicidality are complex and may have some relative specificity for depression, although perhaps more accurately, for hopelessness, one aspect of some depressions (5).

Because depressive symptoms are all relatively nonspecific, it is perhaps not surprising that individual depressive symptoms are widely reported in the general population (Table 2). In the Epidemiologic Catchment Area study, lifetime rates of depressive symptoms range from as low as 5% for anhedonia to 30% for dysphoric mood lasting at least two weeks (6). The Centers for Disease Control's (CDC's) Behavioral Risk Factor Surveillance System (BRFSS), based upon the Patient Health Questionnaire (PHQ-8), found that depressive symptoms lasting at least a week during the previous two weeks ranged from 6-19%; similar findings were observed in the National Health and Nutrition Examination Survey (NHANES) (7). Indeed, in the NHANES survey, 65% of adults reported at least one depressive symptom in the previous week (8). The National Comorbidity Survey and its derivatives (Collaborative Psychiatric Epidemiology Surveys, CPES, www.icpsr.umich.edu/icpsrweb/CPES) found rates up to 9% of various depressive symptoms in the past month. Although there is variability among these epidemiological surveys and some controversy around the best approach to measure depressive symptoms in the general population, it is nonetheless clear that the incidence and prevalence of depressive symptoms are high.

Complicating identification of depressive disorders is a persistent concern about the reliability of assessing these conditions. For example, in the recent DSM-5 field trials across various U.S. sites, test-retest reliability (two clinicians separately evaluating a patient) ranged from very poor (kappa=0.13) to a 'best case' of only fair (kappa=0.42) (9). Moreover, a recently proposed mixed anxiety depressive disorder had an overall kappa<0.20, deemed unacceptable. In contrast, assessment of individual depressive symptoms across diagnoses showed good test-retest reliability (ICC>.60 typically) from the same field trial (10). In the ICD-10 field trial in the US and Canada, similar poor inter-rater reliability were observed for a severe depressive episode (kappa=0.40), a mild depressive episode (kappa=0.33), various recurrent depressive disorders (kappas=.09-.22) and dysthymia (kappa=0.33), although somewhat better reliability was noted in other countries (11). In the past, the DSM-IV field trial had shown similarly poor 6-month test-retest reliability of depressive disorders to the DSM-5 field trial, although somewhat better inter-

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

rater reliability than the ICD-10 field trial (12). These data suggest that although depressive symptoms can be reliably identified, depressive syndromes are more difficult to consistently diagnosis across time and evaluators, increasing the risk that nonspecific expressions of these symptoms across a wide variety of circumstances may be identified as major depression.

Taken together, the nonspecificity of depressive symptoms that are individually very common in the general population coupled with a relatively arbitrary temporal threshold (2 weeks) may contribute to the high rates of the population prevalence of depressive syndromes. Additionally, given the nature of these symptoms, it is likely that they arise from multiple underlying events. These features of how depression is identified are reflected in the limited reliability observed in diagnostic criteria field trials and are consistent with our hypothesis about the nonspecificity of the depressive syndrome.

Major depression is a common comorbidity

Major depression may be the most commonly occurring comorbidity in all of medicine, spanning psychiatric, neurological and other medical conditions. Table 3 lists rates of depression in several common psychiatric conditions; these rates were derived from our best estimates of typically inconsistent rates across articles, with a representative paper referenced. As can be seen, in virtually every psychiatric illness, co-occurring major depression is common with increased risks of 2-5 times (or greater) compared to the general population; in fact, we were unable to identify a psychiatric condition that lacked this increased risk. In essentially every instance, the co-occurrence of depression is associated with poorer outcome, including decreased rates of recovery, increased rates of suicide, and poorer psychosocial function. In bipolar I disorder, although defined by the occurrence of mania, in fact the bulk of clinical management centers on treating depression. Similarly in schizophrenia, which is defined as a ‘non-affective psychotic illness’, depression is a major clinical confound with limited specific treatment strategies. It appears, then, that any psychiatric illness in general represents a risk factor for developing major depression; i.e., depression appears to be a nonspecific response to mental illnesses.

Table 4 lists rates of depression in several common neurological and medical conditions. In people with neurological disorders, studies typically report that depression occurs in 1/3-1/2 of individuals, again a 2-5 times increased risk over the general population. As with psychiatric conditions, depression following stroke or in the courses of epilepsy or other neurologic illnesses is associated with worse outcome and complicated and uncertain treatment decisions. Coupled with the findings in psychiatric disorders, these data suggest that any medical condition that impacts brain function dramatically increases the risk for depression.

The risk for increased depression associated with medical illness appears to transcend those conditions with direct central nervous system etiologies. For example, as listed in Table 4, rates of depression are elevated in major illnesses across multiple organ systems including coronary artery disease, cancer, autoimmune disorders, metabolic disorders and chronic pulmonary and renal disease. There is no identified common underlying mechanism for these associations, although all medical illnesses stress the individual and there is a vast literature demonstrating associations between depression and stress (e.g. 13,14). Indeed, stress may represent a common risk factor for depression across a wide variety of life events. However, the rates of depression in conditions affecting the brain appear to be higher than non-CNS medical conditions, suggesting that these associations are more than just nonspecific stress responses (although perhaps that is an important subset of cases). In summary, then, the risk for major depression appears to increase with virtually any condition

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

that impacts brain function and many other medical illnesses that may indirectly impact brain function or stress the individual, suggesting multiple and nonspecific mechanisms underlying its genesis. That said, the rate of co-occurring depression is not 100% in any of these conditions, so that that other contributing factors must be involved. These might include specific genetic or neurobiological risks as discussed subsequently.

Genetic risk for depression appears to increase with any psychiatric condition

Major depression is familial. As reviewed in their meta-analysis, Sullivan et al. (15) found an elevated risk of major depression in families of a depressed proband (odds ratio=2.84). However, the family studies that comprised this meta-analysis were not able to determine if the increased risk was due to genetics or environment. Adoption studies represent a 'natural experiment' to more specifically address this distinction, and they have provided suggestive, but inconclusive, evidence that depression may have a genetic component (15). Twin studies also provide a means to isolate genetic effects and suggest a heritability rate of 0.31-0.42 for depression in general (15), although this rate may increase to 0.66 in carefully diagnosed recurrent major depression (16). Regardless, heritability rates are lower than in other common psychiatric illnesses (e.g., schizophrenia, bipolar disorder). A number of studies using a wide variety of methods have attempted to identify risk genes for depression, but to date, no gene has withstood the test of multiple studies (17); consequently risk alleles have remained elusive, even for depressive subgroups. Depression therefore appears to arise from both environmental and genetic influences, as well as the interactions between the two risk factors, although a recent paper suggests it is life stress alone, not the interaction, underlying the development of depression (14). A major confound previously discussed, that has not been typically addressed in family or genetic studies, is that depression is commonly comorbid and perhaps caused by a number of other psychiatric and medical illnesses that themselves have complex genetic and environmental risks. Indeed, in an Australian sample, Saha et al (18) found that probands with major depression had increased risks for several different psychiatric and medical disorders, suggesting generalized as opposed to specific shared risk factors.

Consistent with this latter suggestion, family studies of bipolar I disorder probands find a higher risk for major depression than bipolar I disorder, even though the risk for the latter is much more specific; i.e., the risk for bipolar I disorder does not typically increase in families of unipolar depressed probands (19). Moreover, 71% of liability of mania is independent from liability for depression in bipolar I disorder (20), consistent with the notion that depression in bipolar families arises separately from the bipolar risk (i.e., mania risk) *per se* and perhaps is epiphenomenal to the neurobiology that underlies mania. Major depression is also elevated in relatives of probands with other psychiatric and neurological conditions including obsessive-compulsive disorder (21), Parkinson's disease (22), migraine (23), post-traumatic stress disorder (24), and personality disorders (e.g., 25). Indeed, rates of major depression appear to be increased in the family members of most neurological and psychiatric conditions, although many of these associations have not been rigorously studied. Together, the genetic and familial transmission data support the suggestion that major depression is a nonspecific response to multiple underlying sources of brain pathology.

The neurophysiology of depression remains difficult to define

Despite being very common and studied extensively for many years, the specific neurobiology of depression has remained elusive. There are a number of potential reasons for this problem; first and foremost, the human brain is complex (if not we would neither be

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

writing or reading this article, or, in fact, thinking about brain function in the first place). Consequently the workings of the brain even for simple behaviors remains incompletely understood in general. The symptoms and signs of depression suggest that it arises from dysfunction within emotional and cognitive brain networks. As reviewed by Price and Drevets (26), cognitive and emotional neuroscience advances that have clarified the function of these networks have typically arisen within the context of narrowly and specifically defined behaviors within animal models. In contrast, the relatively nonspecific symptoms used to define depression almost guarantee heterogeneous samples of depressive etiologies in most human studies. For example, although anhedonia as defined in DSM-V is useful in general clinical practice, it is much too broad for neuroscience research as it combines elements of inability to experience pleasure, negativity bias and amotivation, all of which have different underlying neural components, but any one of which might be contributing to a depressive subject's inclusion in an imaging study. Similarly, decreased concentration identified clinically may include memory deficits, attentional impairment, or negativity biases at a cognitive level, again implicating different neural systems (26).

The neurophysiological basis of human emotional function remains incompletely described (27). However, animal and human studies suggest that this function is modulated predominantly by two relatively independent prefrontal-striatal-pallidal-thalamic networks (26, 27). The first originates in orbital/ventrolateral prefrontal cortex and appears to 'manage' emotional salience of external stimuli, as this network is strongly connected to a variety of processed sensory brain regions. The second originates in the medial prefrontal cortex and appears to modulate internal mood states, given its connections to hypothalamic and consequently autonomic areas that presumably underlie 'feelings.' It is commonly hypothesized that depression arises from dysfunction within one or both of these networks, and this hypothesis has been generally, although not universally, supported by human studies (e.g., 26-29). A third network, originating in the dorsolateral prefrontal cortex, appears to be reciprocally linked to emotional networks and may consequently underlie cognitive and executive symptoms of depression (26-29). These networks are modulated by monoaminergic systems and replete with glutamate neurotransmission, tying in hypotheses related to the known function of approved and putative antidepressant therapies. The medial prefrontal network's hypothalamic connections likely reflect the longstanding and well-described abnormalities in cortisol function in some depressed subjects (26). Confounding these models somewhat is recent evidence that the best predictor of treatment response for major depression is activation in the anterior insula, a brain region typically associated with the disgust response that is not directly part of these prefrontal-striatal-thalamic-pallidal loops, although is connected (30).

Importantly, similar functional neuroanatomic models have been described for a variety of behavioral conditions that impact emotional and cognitive function including, for example, Parkinson's disease (31), bipolar disorder (27), schizophrenia (32), obsessive-compulsive disorder (33), Alzeheimer's disease (34), post-traumatic stress disorder (35) and personality disorders (36). This nonspecificity of the model largely reflects the incomplete understanding of these networks within the human brain. However, it is also consistent with a hypothesis that depression is an epiphenomenon of dysfunction within these systems independent of the specific underlying cause, e.g., stroke, traumatic brain injury, aberrant personality development, psychological trauma/stress or bipolar disorder.

Depression responds to a nonspecific range of treatments (including placebo)

Many people who struggle with depression also struggle to find effective treatment. Indeed, only 50% of treated depressed individuals achieve full remission (37). Our inability to

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

establish more effective treatments may be another indication that there are several types of depression (38) or that depression is a nonspecific response to a variety of underlying conditions. Treatment-related factors that suggest depression develops via multiple pathways include the effectiveness of a wide range of interventions, the multi-system disorders for which “antidepressants” are effective, the high response rate to placebo, and the lack of a consistent pathophysiologic model to explain the therapeutic effects of interventions.

Standard of care for the treatment of depression generally involves both psychotherapeutic and pharmacologic interventions. However, depression is equally responsive (and non-responsive) to a wide variety of interventions, including placebo, suggesting that more than a single underlying illness is being treated. There are several types of evidence-based psychotherapeutic options for depression (e.g. cognitive behavioral therapy or interpersonal therapy). However, these interventions vary considerably in many aspects, including theoretical basis, duration, and modality (39, 40). Despite these differences, rates of effectiveness are similar among most of these psychotherapeutic strategies, yet it remains difficult to predict which individual will respond to which approach.

First-line pharmacologic intervention generally involves a selective serotonin reuptake inhibitor (SSRI). However, there are several other classes of antidepressant medications, such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), as well as the newer norepinephrine dopamine reuptake inhibitors (NDRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) that are commonly used to treat depressive symptoms. More recently, the efficacy of second generation antipsychotics, as monotherapy or adjunctive therapy, has also been demonstrated. Despite variability in the proposed mechanisms of action, response rates are similar across the different classes of pharmacologic interventions (41, 42), although, again, predicting individual response is not possible. Moreover, there are several additional treatments that have comparable efficacy, such as deep brain stimulation (DBS), sleep deprivation, acupuncture, omega-3 fatty acid supplementation, St. John’s Wart, and exercise. Indeed, perhaps the most effective antidepressant, electroconvulsive therapy (ECT) is also the least specific, as response is related to seizure induction. Although a common underlying mechanism of action for these widely varying treatment strategies has yet to be determined, and we would posit, probably does not exist, a potential explanation for how these diverse and often non-specific treatments lead to a similar response is that depression is not a single unique disorder (38). In other words, while the clinical manifestations may be similar, the underlying pathophysiologies may differ among those who respond to one type of intervention vs. those who respond to a different treatment strategy. The nonspecificity of treatments and treatment response support the suggestion that depression may be simply an epiphenomenal response to a wide variety of brain insults and injury.

In addition to the lack of specificity of treatments, most of the pharmacotherapies used for depression are also effective for several other disorders that involve many systems of the body. For example, antidepressants are commonly used for anxiety disorders, neuropathic pain, premenstrual dysphoric disorder, substance use disorders, and irritable bowel syndrome, providing further evidence that depression may be a non-specific manifestation of a wide variety of conditions.

Considerable debate has occurred regarding the efficacy of antidepressants for treating major depression because of the high placebo response rates observed in many studies (43). Indeed, several meta-analyses indicate that antidepressants are equivalent to placebo for treating mild to moderate depression (44-46). It has been proposed that “common factors”, such as expectancy effects and non-specific psychotherapeutic and supportive impact of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

interactions with study clinicians, contribute to the meaningful responses that occur in patients with depressive symptoms (39). Regardless, the large placebo response reported in clinical trials of antidepressants provides additional support for the lack of specificity of interventions that lead to improvement in depressive symptoms.

Available treatments for depression are suboptimal, in part, because the underlying pathophysiologic actions of current treatments are poorly understood. Moreover, preclinical models for testing the effects of potential antidepressants are primarily based upon learned helplessness or chronic stress models that are themselves non-specific, and differ in the degree to which they produce features that resemble a depressive-like state (38, 47). With these preclinical models underlying most antidepressant development, one wonders whether our modern antidepressants may be more accurately viewed as 'anti-stress disorder' medications.

Nonetheless, several hypotheses of how antidepressants work have been proposed, including the monoamine hypothesis, dysfunctional cortisol and hypothalamic-pituitary axis (HPA) axis, altered neuroimmune and inflammatory processes, dysfunctional circadian rhythms, and glutamatergic dysregulation (37, 48-50). The monoamine hypothesis, which is based on the efficacy of MAOIs, tricyclic antidepressants and SSRIs, suggests an imbalance of serotonergic and noradrenergic neurotransmitters. More recently, the efficacy of mixed serotonergic-norepinephrine reuptake inhibitors (SNRIs) has been demonstrated. However, 30-50% of patients treated with these medications do not show significant clinical improvement. Moreover, the monoamine receptor effects of these drugs occur essentially immediately, yet clinical response takes weeks. These observations suggest the monoamine hypothesis is insufficient.

There is a well-established relationship between stressful life events and depression. Indeed, as noted, preclinical models use for antidepressant development are really stress models. The HPA axis is involved in modulating the stress response and therefore, dysfunction within this pathway is likely involved in depression. Indeed, HPA hyperactivity is evident in depressed patients, as demonstrated by abnormalities in the dexamethasone suppression test. However, whether these alterations are a risk factor for or consequence of depression remains unclear. Related, abnormalities in inflammatory cytokines, which may lead to decreased serotonin synthesis, have been demonstrated in patients with depression. Some antidepressants have been shown to reduce inflammation through inhibition of the release of cytokines. Alterations in sleep and appetite are common depressive symptoms and circadian rhythm genes are responsible for regulation of these functions. Treatments that involve modulation of clock genes, such as fluoxetine, agomelatine, and sleep deprivation are effective for depression. Finally, the rapid antidepressant effect of ketamine, an NMDA receptor antagonist, appears to result from a direct impact on glutamatergic signaling (45). Although the proposed effects of antidepressants involve endocrine, inflammatory, circadian rhythm and other processes related to neurotransmitter metabolism, such as epigenetics and neuroplasticity, the lack of specificity of these mechanisms of action suggests that multiple pathways are involved in the pathogenesis of depression. Again, together, these data further support the notion that depression may simply represent a nonspecific behavioral response to a wide variety of underlying neurological conditions.

Conclusions

A wide variety of considerations and data suggest that depression represents a nonspecific symptomatic response to a number of underlying conditions. If this hypothesis is correct, what does it say about how we approach depression? From a clinical standpoint, it suggests that efforts to identify underlying risk factors, e.g., other neurological or psychiatric

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

disorders or acute life stressors, should take first priority and then treatment must be developed to manage the underlying condition first and the depressive symptoms second. Along these same lines, then, focused treatment development studies are needed in well-defined subgroups, e.g., bipolar depression, depression following severe stress, or depression in the context of migraines, in order to determine what types of interventions are most effective for those specific individuals. Moreover, as clinical studies of depression are performed, much more care must be incorporated to eliminate diverse risk factors for depression that may increase subject heterogeneity.

From a clinical neuroscience perspective, subject identification and recruitment will need to identify these same types of etiological subgroups to focus genetic, neuroimaging and other studies to begin to identify what neuropathological events lead to this nonspecific behavioral response. Additionally, as has been proposed by the NIMH, developing research domain criteria that define more objective and replicable endophenotypes within subgroups of individuals at risk for depression may help to better understand the contributing behavioral neurobiology. As these neurobiological underpinnings of subgroups and dimensions of depression are better understood within the context of more homogeneous groups, better models for treatment development are inevitable. By taking an approach that assumes depression is epiphenomenal, rather than primary, it will force us to pay closer attention to the multiple confounds underlying any human population, while refining considerations for treatment development. Doing so may lead to a more productive approach to managing these pervasive and common syndromes.

REFERENCES

Recently published papers of particular interest have been highlighted as:

* Of importance

** Of major importance

1. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS, National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289:3095–3105. [PubMed: 12813115]
2. World Health Organization. The World Health Report 2002: Reducing Risks, Promoting Healthy Life. World Health Organization; Geneva, Switzerland: 2002.
3**. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (Fifth ed.). 2013American Psychiatric Publishing Inc.Arlington, VA The DSM-5 alters a number of features about psychiatric diagnoses, namely by removing the 3-axis system, which might be particularly relevant to this article, since medical and psychiatric diagnoses are now treated similarly.
4. World Health Organisation. ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines. World Health Organisation; Geneva: 1992.
5. Malone KM, Oquendo MA, Haas GL, Ellis SP, Li S, Mann JJ. Protective factors against suicidal acts in major depression: reasons for living. Am J Psychiatry. 2000; 157:1084–1088. [PubMed: 10873915]
6. Weissman, MM.; Bruce, ML.; Leaf, PJ.; Florio, LP.; Holzer, C. Affective disorders. In: Robins, LN.; Regier, DA., editors. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. The Free Press; NY, NY: 1991. p. 53-80.
7. Li C, Ford ES, Guixiang Z, Tsai J, Balluz LS. A comparison of depression prevalence estimates measured by the Patient Health Questionnaire with two administration modes: computer-assisted telephone interviewing versus computer-assisted personal interviewing. Int J Public Health. 2012; 57:225–233. [PubMed: 21523617]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

8. Wight RG, Sepulveda JE, Aneshensel CS. Depressive symptoms: How do adolescents compare with adults. J Adol Health. 2004; 34:314–323.

9*. Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, Kupfer DJ. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry. 2013; 170:59–70. [PubMed: 23111466] This and its companion papers demonstrate the ongoing difficulty psychiatry has developing reliable diagnostic criteria sets in the setting of field trials. However, in more structured research environments, reliability tends to be quite a bit higher for most conditions.

10*. Narrow WE, Clarke DE, Kuramoto SJ, Kraemer HC, Kupfer DJ, Greiner L, Regier DA. DSM-5 field trials in the United States and Canada, Part III: development and reliability testing of a cross-cutting symptom assessment for DSM-5. Am J Psychiatry. 2013; 170:71–82. [PubMed: 23111499] This and its companion papers demonstrate the ongoing difficulty psychiatry has developing reliable diagnostic criteria sets in the setting of field trials. However, in more structured research environments, reliability tends to be quite a bit higher for most conditions.

11. Regier DA, Kaelber CT, Roper MT, Rae DS, Sartorius N. The ICD-10 clinical field trial for mental and behavioral disorders: results in Canada and the United States. Am J Psychiatry. 1994; 151:1340–1350. [PubMed: 8067491]

12. Keller MB, Klein DN, Hirschfeld RM, Kocsis JH, McCullough JP, Miller I, First MB, Holzer CP 3rd, Keitner GI, Marin DB, et al. Results of the DSM-IV mood disorders field trial. Am J Psychiatry. 1995; 152:843–849. [PubMed: 7755112]

13. Kendler KS, Kessler RC, Walters EE, MacLean CJ, Neale MC, Heath AC, Eaves LJ. Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry. 1995; 152:833–842. [PubMed: 7755111]

14. Gillespie NA, Whitfield JB, Williams B, Heath AC, Martin NG. The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. Psychol Med. 2005; 35:101–111. [PubMed: 15842033]

15. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000; 157:1552–1562. [PubMed: 11007705]

16. Foley DL, Neale MC, Kendler KS. Reliability of a lifetime history of major depression: implications for heritability and comorbidity. Psychol Med. 1998; 28:857–870. [PubMed: 9723141]

17. Bosker FJ, Hartman CA, Nolte IM, Prins BP, Terpstra P, Posthuma D, van Veen T, Willemsen G, DeRijk RH, de Geus EJ, Hoogendijk WJ, Sullivan PF, Penninx BW, Boomsma DI, Snieder H, Nolen WA. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Molec Psychiatry. 2011; 16:516–532. [PubMed: 20351714]

18. Saha S, Stedman TJ, Scott JG, McGrath JJ. The co-occurrence of common mental and physical disorders within Australian families: A national population-based study. Aust N Z J Psychiatry. Apr 29.2013 Epub ahead of print.

19. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Gen C. 2003; 123C:48–58.

20. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry. 2003; 60:497–502. [PubMed: 12742871]

21. Nestadt G, Samuels J, Riddle MA, Liang KY, Bienvenu OJ, Hoehn-Saric R, Grados M, Cullen B. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. Psychol Med. 2001; 31:481–487. [PubMed: 11305856]

22. Arabia G, Grossardt BR, Geda YE, Carlin JM, Bower JH, Ahlskog JE, Maraganore DM, Rocca WA. Increased risk of depressive and anxiety disorders in relatives of patients with Parkinson disease. Arch Gen Psychiatry. 2007; 64:1385–1392. [PubMed: 18056546]

23. Merikangas KR, Merikangas JR, Angst J. Headache syndromes and psychiatric disorders: association and familial transmission. J Psychiatr Res. 1993; 27:197–210. [PubMed: 8366469]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

24. Flory JD, Yehuda R, Passarelli V, Siever LJ. Joint Effect of Childhood Abuse and Family History of Major Depressive Disorder on Rates of PTSD in People with Personality Disorders. Depress Res Treat. 2012:ID350461. e-journal.

25. Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. J Pers Disord. 2003; 17:233–242. [PubMed: 12839102]

26*. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. Trends Cogn Sci. 2012; 16:61–71. [PubMed: 22197477] This article is a very well-written review of the functional neuroanatomy of human emotions and mood conditions.

27*. Strakowski SM. Strakowski SM. Integration and consolidation: a neurophysiological model of bipolar disorder. The Bipolar Brain: Integrating Neuroimaging and Genetics. 2012Oxford University Press, Inc.NY, NY This chapter is one in a text dedicated to integrating neuroimaging and genetics in bipolar disorder. The book provides a very comprehensive review from a number of the world's leading experts in the study of bipolar disorder.

28. Sacher J, Neumann J, Funfstuck T, Soliman A, Villringer A, Schroeter ML. Mapping the depressed brain: A meta-analysis of structural and functional alterations in major depressive disorder. J Aff Dis. 2012:142–148.

29. Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res. 2009; 201:239–243. [PubMed: 19428640]

30*. McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR, Craddock RC, Mayberg HS. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry. 2013; 12:1–9. This article is a well-done idea paper to challenge the study of and treatment development for depression.

31. Sudhyadhom A, Bova FJ, Foote KD, Rosado CA, Kirsch-Darrow L, Okun MS. Limbic, associative, and motor territories within the targets for deep brain stimulation: potential clinical implications. Curr Neurol Neurosci Rep. 2007; 7:278–289. [PubMed: 17618533]

32. Goghari VM, Sponheim SR, MacDonald AW 3rd. The functional neuroanatomy of symptom dimensions in schizophrenia: a qualitative and quantitative review of a persistent question. Neurosci Biobehav Rev. 2010; 34:468–486. [PubMed: 19772872]

33. Saxena S, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am. 2000; 23:563–586. [PubMed: 10986728]

34. Andreescu C, Aizenstein H. MRI studies in late-life mood disorders. Curr Top Behav Neurosci. 2012; 11:269–87. [PubMed: 22167336]

35. Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: a critical review. Prog Brain Res. 2008; 167:151–69. [PubMed: 18037013]

36. Mauchnik J, Schmahl C. The latest neuroimaging findings in borderline personality disorder. Curr Psychiatry Rep. 2010; 12:46–55. [PubMed: 20425310]

37. Massart R, Mongeau R, Lanfumey L. Beyond the monoaminergic hypothesis: neuroplasticity and epigenetic changes in a transgenic mouse model of depression. Philos Trans R Soc Lond B Biol Sci. 2012; 367:2485–2494. [PubMed: 22826347]

38. Forgeard MJ, Haigh EAP, Beck AT, Davidson RJ, Henn FA, Maier SF, Mayberg HS, Seligman MEP. Beyond depression: Toward a process-based approach to research, diagnosis, and treatment. Clin Psychol. 2011; 18:275–299.

39. Alladin A. The power of belief and expectancy in understanding and management of depression. American Journal of Clinical Hypnosis. 2012; 55:249–271.

40. Nieuwsma JA, Trivedi RB, McDuffie J, Kronish I, Benjamin D, Williams JW. psychotherapy for depression: a systematic review and meta-analysis. Int J Psychiatry Med. 2012; 43:129–151. [PubMed: 22849036]

41. Artigas F, Nutt DJ, Shelton R. Mechanism of action of antidepressants Psychopharmacol. Bull. 2002; 2:123–132. 36 Suppl.

42. Cipriani A, Koesters M, Furukawa TA, Nosè M, Purgato M, Omori IM, Trespidi C, Barbui C. Duloxetine versus other anti-depressive agents for depression. Cochrane Database Syst Rev. Oct 17.2012

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

43. Preskorn SH. Declining differences in response rates with antidepressants versus placebo: A modest proposal for another contributing cause. J Psychiatr Pract. 2013; 19:227–233. [PubMed: 23653079]
44. Iovieno N, Papakostas GI. Correlation between different levels of placebo response rate and clinical trial outcome in major depressive disorder: a meta-analysis. J Clin Psychiatry. 2012; 73:1300–1306. [PubMed: 23140647]
45. Andrade C. There's more to placebo-related improvement than the placebo effect alone. J Clin Psychiatry. 2012; 73:1322–1325. [PubMed: 23140650]
46. Leucht C, Huhn M, Leucht S. Amitriptyline versus placebo for major depressive disorder. Cochrane Database Syst Rev. Dec 12.2012
47. Duman CH. Models of depression Vitam Horm. 2010; 82:1–21.
48*. Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: The path to ketamine and beyond. Biol Psychiatry. 2013; 73:1133–1141. [PubMed: 23726151] This article present a review of novel potential antidepressants based on glutamatergic neurotransmission; as noted in the current article, novel approaches are sorely needed.
49. Pilc A, Wieronska JM, Skolnick P. Glutamate-based antidepressants: Preclinical psychopharmacology. Biol Psychiatry. 2013; 73:1125–1132. [PubMed: 23453290]
50. Bunney BG, Bunney WE. Mechanisms of rapid antidepressant effects of sleep deprivation therapy; clock genes and circadian rhythms. Biol Psychiatry. 2013; 73:1164–1171. [PubMed: 22906517]
51. Goodwin, FK.; Jamison, KR. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. Oxford University Press, Inc.,; NY, NY: p. 13-15.
52. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull. 2009; 35:383–402. [PubMed: 19011234]
53. Karno, M.; Golding, JM. Obsessive compulsive disorder. In: Robins, LN.; Regier, DA., editors. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. The Free Press; NY, NY: 1991. p. 204-219.
54. Kessler RC, Stang PE, Wittchen HU, Ustun TB, Roy-Burne PP, Walters EE. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Arch Gen Psychiatry. 1998; 55:801–808. [PubMed: 9736006]
55. Judd LL, Kessler RC, Paulus MP, Zeller PV, Wittchen HU, Kunovac JL. Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). Acta Psychiatr Scand Suppl. 1998; 393:6–11. [PubMed: 9777041]
56. Breslau N, Davis GC, Andreski P, Peterson E. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry. 1991; 48:216–222. [PubMed: 1996917]
57. Klassen LJ, Katzman MA, Chokka P. Adult ADHD and its comorbidities, with a focus on bipolar disorder. J Affect Disord. 2010; 124:1–8. [PubMed: 19683348]
58. Schuckit MA. Comorbidity between substance use disorders and psychiatric conditions. Addiction. 2006; 101(Suppl 1):76–88. [PubMed: 16930163]
59. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006; 67:247–257. [PubMed: 16566620]
60. Lenzenweger M, Lane M, Loranger A, Kessler RC. Personality disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007; 62:553–564. [PubMed: 17217923]
61. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, Smith SM, Dawson DA, Pulay AJ, Pickering RP, Ruan WJ. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2008; 69:533–545. [PubMed: 18426259]
62. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br J Psychiatry. 2013; 202:14–21. [PubMed: 23284148]
63. Strober LB, Arnett PA. Assessment of depression in three medically ill, elderly populations: Alzheimer's disease, Parkinson's disease, and stroke. Clin Neuropsychol. 2009; 23:205–230. [PubMed: 18609323]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

64. Barry JJ, Ettinger AB, Friel P, Gilliam FG, Harden CL, Hermann B, Kanner AM, Caplan R, Plioplys S, Salpekar J, Dunn D, Austin J, Jones J, Advisory Group of the Epilepsy Foundation as part of its Mood Disorder. Consensus statement: the evaluation and treatment of people with epilepsy and affective disorders. Epilepsy Behav. 2008; 13(Suppl 1):S1–29. [PubMed: 18502183]
65. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008; 23:183–189. [PubMed: 17987654]
66. Modrego PJ. Depression in Alzheimer's disease: Pathophysiology, diagnosis, and treatment. J Alzheimers Dis. 2010; 21:1077–1087. [PubMed: 21504132]
67. Siegert RJ, Abernethy DA. Depression in multiple sclerosis: a review. J Neurol Neurosurg Psychiatry. Apr; 2005 76(4):469–75. [PubMed: 15774430]
68. Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB. Psychiatric comorbidities of episodic and chronic migraine. J Neurol. Nov 7.2012 Epub ahead of print.
69. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. Cardiovasc Psychiatry Neurol. 2013 Epub ahead of print.
70. Norwood R. Prevalence and impact of depression in chronic obstructive pulmonary disease patients. Curr Opin Pulm Med. 2006; 12:113–117. [PubMed: 16456380]
71. Kimmel PL, Cukor D, Cohen SD, Peterson RA. Depression in end-stage renal disease patients: a critical review. Adv Chronic Kidney Dis. 2007; 14:328–334. [PubMed: 17904499]
72. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, Meader N. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011; 12:160–174. [PubMed: 21251875]
73. Joyce AT, Smith P, Khandker R, Melin JM, Singh A. Hidden cost of rheumatoid arthritis (RA): estimating cost of comorbid cardiovascular disease and depression among patients with RA. J Rheumatol. 2009; 36:743–752. [PubMed: 19228658]
74. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord. 2012; 142(Suppl):S8–21. [PubMed: 23062861]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

DSM-5 criteria for depression, paraphrased for brevity (3).

Five or more of the following symptoms/signs must occur most of the day nearly every day for at least 2 weeks and represent a change from previous function. Depressed mood or anhedonia must be present as one of the five:
1 Depressed mood;
2 Anhedonia;
3 Significant change in weight or appetite;
4 Insomnia or hypersomnia;
5 Psychomotor agitation or retardation;
6 Fatigue;
7 Feelings of worthlessness or excessive guilt;
8 Diminished concentration or indecisiveness;
9 Recurrent thoughts of death or suicidality.
The symptoms must cause significant distress and/or functional impairment. The episode cannot be better explained by the effects of a substance or other medical or psychiatric condition. There is no history of mania.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Lifetime prevalence of selected depressive symptoms from epidemiologic surveys.

Symptom	ECA lifetime	BRFSS current	CPES current	NHANES current
Dysphoria	30	7	8	5
Appetite Change	24	11	n/a	6
Sleep change	23	17	9	12
Psychomotor change	9	4	2	4
Loss of interest	5	9	5	5
Fatigue	16	19	9	14
Guilt/worthless	11	6	9	6
Diminished concentration	14	6	6	6
Death thoughts	28	n/a	n/a	n/a

ECA=Epidemiological Catchment Area study (6); BRFSS=Behavioral Risk Factor Surveillance System (7); CPES=Collaborative Psychiatric Epidemiology Surveys (www.icpsr.umich.edu/icpsrweb/CPES); NHANES= National Health and Nutrition Examination Survey (7).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 3

Lifetime prevalence of co-occurring major depression in common psychiatric disorders.

Condition	Rate of depression	Selected references
Bipolar I disorder	90%	51
Schizophrenia	50%	52
OCD	30%	53
Panic disorder	50%	54
GAD	67%	55
PTSD	37%	56
ADHD	25%	57
Alcohol use disorders	40%	58
Drug use disorders	40%	59
Borderline PD	30%	60, 61
Personality disorders	23%	60, 61

OCD=obsessive-compulsive disorder; GAD=generalized anxiety disorder; PTSD=post-traumatic stress disorder; ADHD=attention deficit hyperactivity disorder; PD=personality disorder.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 4

Lifetime prevalence of co-occurring major depression in common neurological and other medical disorders.

Condition	Rate of depression	Selected references
NEUROLOGIC		
Stroke	30%	62, 63
Epilepsy	35%	64
Parkinson's disease	40%	63, 65
Alzheimer's disease	50%	63, 66
Multiple sclerosis	50%	67
Migraine	47%	68
OTHER MEDICAL		
Cardiovascular disease	35%	69
COPD	40%	70
Chronic kidney disease	30%	71
Cancer	30%	72
Rheumatoid arthritis	20%*	73
Diabetes	33%	74

COPD=chronic obstructive pulmonary disease

*current, rather than lifetime, risk.