Curr Psychiatry Rep (2013) 15:386
DOI 10.1007/s11920-013-0386-z

Is Depression Simply a Nonspecific Response to Brain Injury?

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Published online: 14 August 2013

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 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.

This article is part of the Topical Collection on *Mood Disorders*

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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

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.

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.

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]

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 was 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-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 disorders. 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., [37, 38]). 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 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 other contributing factors must be involved. These might include specific genetic or neurobiological risks as discussed subsequently.

Table 3 Lifetime prevalence of co-occurring major depression in common psychiatric disorders

Condition	Rate of depression	Selected references
Bipolar I disorder	90 %	[13]
Schizophrenia	50 %	[14]
OCD	30 %	[15]
Panic disorder	50 %	[16]
GAD	67 %	[17]
PTSD	37 %	[18]
ADHD	25 %	[19]
Alcohol use disorders	40 %	[20]
Drug use disorders	40 %	[21]
Borderline PD	30 %	[22, 23]
Personality disorders	23 %	[22, 23]

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

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 %	[24, 25]
Epilepsy	35 %	[26]
Parkinson's disease	40 %	[25, 27]
Alzheimer's disease	50 %	[25, 28]
Multiple sclerosis	50 %	[29]
Migraine	47 %	[30]
Other medical		
Cardiovascular disease	35 %	[31]
COPD	40 %	[32]
Chronic kidney disease	30 %	[33]
Cancer	30 %	[34]
Rheumatoid arthritis	20 %*	[35]
Diabetes	33 %	[36]

*current, rather than lifetime, risk

COPD=chronic obstructive pulmonary disease

Genetic Risk for Depression Appears to Increase with Any Psychiatric Condition

Major depression is familial. As reviewed in their meta-analysis, Sullivan et al. [39] 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 [39]. Twin studies also provide a means to isolate genetic effects and suggest a heritability rate of 0.31-0.42 for depression in general [39], although this rate may increase to 0.66 in carefully diagnosed recurrent major depression [40]. 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 [41]; 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 these two risk factors, although a recent paper suggests it is life stress alone, not the interaction, underlying the development of depression [38]. 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. [42] 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 [43]. Moreover, 71 % of liability of mania is independent from liability for depression in bipolar I disorder [44], 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 [45], Parkinson's disease [46], migraine [47], post-traumatic stress disorder [48], and personality disorders (e.g., [49]). 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 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 [50•], 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 [50•].

The neurophysiological basis of human emotional function remains incompletely described [51•]. However, animal and human studies suggest that this function is modulated predominantly by two relatively independent prefrontal-striatal-pallidal-thalamic networks [50•, 51•]. The first originates in 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., [50•, 51•, 52, 53]). 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 [50•, 51•, 52, 53]. 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 [50•]. 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 it is connected [54•].

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 [55], bipolar disorder [51•], schizophrenia [56], obsessive-compulsive disorder [57], Alzeheimer's disease [58], post-traumatic stress disorder [59] and personality disorders [60]. This nonspecificity of the model largely reflects 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 [61]. Our inability to establish more effective treatments may be another indication that there are several types of depression [62] 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 [63, 64]. 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 [65, 66], 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 [62]. In other words, while the clinical manifestations may be similar, the underlying pathophysiologies 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 [67]. Indeed, several meta-analyses indicate that antidepressants are equivalent to placebo for treating mild to moderate depression [68–70]. It has been proposed that "common factors", such as expectancy effects and non-specific psychotherapeutic and supportive impact of interactions with study clinicians, contribute to the meaningful responses that occur in patients with depressive symptoms [63]. 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 [62, 71]. 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 [61, 72•, 73, 74]. 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 [69]. 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 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.

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 has received research support from AstraZeneca, Amylin, Eli Lilly, GlaxoSmithKline, Lundbeck, Martek, Merck, Novartis, Otsuka, Pfizer, Takeda, and Shire and has received honoraria for serving on the speakers bureau for Merck.

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.

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- • Of importance
- •• Of major importance

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