DEPRESSION: Mind and Body

Advances in the Understanding and Treatment of Depression and its Physical Symptoms

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Irritable Bowel Syndrome and Depression
Emeran A Mayer and Sylvie Bradesi

Neurostimulation Therapies for Depression: Acute and Long-Term Outcomes
Margaret C Wyche, John O’Reardon, and Linda L Carpenter

Perinatal Depression: A Review
Shaila Misri and Karen Joe

Meeting Report
160th Annual Meeting of the APA

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Clinical Reviews - The most important articles from the best of the international literature on depression are systematically selected by an internationally recognized panel of experts. The Editors then prepare concise and critical analyses of each paper, and, most importantly, place the findings into clinical context.

Meeting Reports - Depression: Mind and Body also provides incisive reporting from the most important international congresses.

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Meeting Report
160th Annual Meeting of the American Psychiatric Association (APA) San Diego, CA, USA
The frequent association of functional gastrointestinal (GI) symptoms with increased anxiety and symptom-related fears, as well as their comorbidity with disorders of mood and affect, is well known to the experienced clinician in both psychiatry and gastroenterology. However, despite extensive epidemiological support for this clinical observation [1], the exact nature of the inter-relationship between functional, somatic, and psychiatric disorders remains to be determined. The constellation of GI symptoms referred to as irritable bowel syndrome (IBS), and related, so-called functional GI disorders (e.g. functional dyspepsia, non-cardiac chest pain), may be regarded from the psychiatrist’s viewpoint as symptoms expected to be associated with certain affective states and the underlying neurobiological dysregulation. However, the majority of gastroenterology research has, until recently, been focused on identifying pathomechanisms specific to the gut, such as altered physiology of smooth muscle, the enteric nervous system, or, more recently, altered mucosal immune function or alterations in host microbial interactions in the gut. It has only been during the past decade that a convergence of research into brain–gut interactions, and the effect of stress on such pathways, has provided a scientific framework to explain the close relationship of brain–gut interactions and emotion, and that of functional GI symptoms and affective disorders [2].

Bidirectional brain–gut interactions play an important role in the regulation of many vital functions in health and disease. In health, brain–gut interactions play a crucial part not only in the regulation of digestive processes (including appetite and food intake), but also in the modulation of the gut-associated immune system and in the coordination of the overall physical and emotional state of the organism with activity in the GI tract (Fig. 1; reviewed in [3]). The strategic location of enterochromaffin cells (ECCs) – loaded with serotonin (5-HT), corticotrophin-releasing factor (CRF), cholecystokinin, and other signaling molecules – at the interface between the microbiome (the 10–100 trillion microorganisms of our gut flora) and the afferent branch of the vagal homeostatic system (with its modulatory influence on a wide range of functions including mood and pain sensitivity), leads us to speculate that microbial–gut–brain signaling may play an important role in our background emotions and general well-being. In disease, altered brain–gut interactions have been proposed as a plausible mechanism underlying symptom generation in functional GI disorders (FGIDs) [4], as well as in the pathophysiology of various eating disorders [5].

**Epidemiology**

**Prevalence of FGIDs**

The hallmark symptoms of IBS are chronically recurrent abdominal pain and discomfort associated with alterations in bowel habits [6]. Different sets of diagnostic criteria have been proposed by international committees of experts to

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**Irritable Bowel Syndrome and Depression**

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Center for Neurovisceral Sciences & Women’s Health, Departments of Medicine, Physiology and Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

The association of functional pain disorders with psychiatric symptoms and afflictions has long been recognized by clinicians. In the case of irritable bowel syndrome (IBS), extensive epidemiological data support an association with depression, anxiety disorders, and somatization. Even though the association is strongest in clinical samples, it has also been observed in population samples, and a psychiatric diagnosis often precedes the diagnosis of IBS. IBS and depression share certain etiological and pathophysiological features, including an important role played by genetic factors, early life environment interactions, and stress sensitivity, a likely involvement of altered serotonin signaling, and a possible role of altered neuroimmune interactions in the central nervous system. The effectiveness of cognitive–behavioral therapeutic approaches has been demonstrated in controlled studies. The most widely used pharmacological therapies for IBS are centrally acting drugs, in particular low dose tricyclic antidepressants. Newer treatment approaches that have been proposed or are in early development include non-selective monoamine reuptake inhibitors, as well as antagonists for neurokinin receptors and corticotrophin-releasing factor 1 receptor. *Depression: Mind and Body* 2007;3(3):94–105.

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define the constellation of these hallmark symptoms as a distinct syndrome, separate from other functional disorders without pain, and from chronic abdominal pain disorders. The most recent version of this definition, the ROME III criteria, has recently been published and is shown in Table 1 [7]. IBS is the most common FGID, with worldwide prevalence rates ranging from 9–23% [8]. Several population-based studies have demonstrated IBS symptoms to be more common in women, with prevalence ratios ranging from 2:1–3:1 [9]. Based on different epidemiological studies performed in different countries, 20–75% of individuals meeting symptom criteria for IBS will seek medical care for their symptoms at some point [10–12].

**Table 1.** Diagnostic criterion for irritable bowel syndrome.
(Criterion must be fulfilled for the previous 3 months with symptom onset ≥6 months prior to diagnosis).

<table>
<thead>
<tr>
<th>Recurrent abdominal pain or discomfort ≥3 days per month in the previous 3 months with two or more of the following:</th>
</tr>
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<tbody>
<tr>
<td>• Improvement with defecation</td>
</tr>
<tr>
<td>• Onset associated with a change in frequency of stool</td>
</tr>
<tr>
<td>• Onset associated with a change in form (appearance) of stool</td>
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Reproduced from [7] with permission of the Rome Foundation.
Prevalence of disorders of mood and affect in IBS

IBS patients report scores of depression and anxiety that are intermediate between psychiatric populations and healthy controls. Even though the presence (and severity) of the psychological distress relates to healthcare-seeking status, it is also observed in so-called non-consulters.

Treatment-seeking samples

Published data on the proportion of clinical IBS patients with psychiatric diagnoses has recently been summarized by Creed et al. [13], and selected prevalence figures from studies using standardized psychiatric research interviews are shown in Table 2. Consistent with earlier reports [21], these reveal that 40–60% of patients with IBS seen in gastroenterology clinics have psychiatric disorders. The proportion of patients entering treatment trials who have psychiatric disorders is similar [22]. The high prevalence of affective disorders in clinical samples of IBS patients could be a reflection of a high rate of comorbidity in all affected patients, a manifestation of the “self-selection hypothesis” [23], or a combination of both phenomena. The first possibility would be expected if the neurobiological mechanisms underlying affective disorders are related to and overlap with central alterations involved in the generation of IBS symptoms. The self-selection hypothesis states that only those patients with the most severe and refractory IBS symptoms are selected into tertiary referral clinics, including for psychiatric referrals. Finally, the involvement of both phenomena would indicate that while IBS and affective disorders do share common central pathophysiological mechanisms, affective disorders such as depression, anxiety, and somatization by themselves will influence healthcare-seeking behavior, regardless of the comorbid medical disorder [24,25].

Population-based samples

Lydiard et al. surveyed the prevalence of GI symptoms (including an IBS “composite” of such symptoms) in individuals with psychiatric disorders in a national community survey of 13,537 respondents (the NIMH ECA [National Institute of Mental Health Epidemiologic Catchment Area] study) [26]. Patients with panic disorder had the highest rate of unexplained GI symptoms (7.2%) compared with the other diagnostic categories, with nearly a five-fold increased likelihood for persons with panic disorder to have the IBS-like composite of symptoms compared with persons without this disorder. Walker et al. reviewed structured psychiatric interviews from nearly 19,000 subjects from the NIMH ECA study for prevalence of GI distress symptoms and selected psychiatric disorders [27]. The prevalence of unexplained GI symptoms in this sample of the general population ranged from 6–25%. Subjects who reported two GI symptoms had significantly higher lifetime prevalence rates for depression, panic, and agoraphobia compared with those who had no reported GI symptoms. In summary, the findings of these studies strongly suggest an association of affective disorders with functional GI symptoms in subjects not seeking healthcare for their abdominal symptoms, and provide evidence to reject a simple self-selection hypothesis.

Anxiety versus depression in different IBS samples

The relative prevalence of anxiety and depression varies significantly in different patient populations [22]. For example, while symptomatic volunteers for treatment studies typically have milder psychiatric disorders (phobias, anxiety) [28], a greater proportion of refractory GI clinic attendees suffer depressive disorders [29]. Patients with IBS recently referred to a gastroenterology practice reported a greater number of symptoms of anxiety than depression [30,31], whereas in

<table>
<thead>
<tr>
<th>Study [ref]</th>
<th>Subjects</th>
<th>Psychiatric interview</th>
<th>FBD</th>
<th>Organic gastrointestinal disorder</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald and Boucher 1980 [14]</td>
<td>FBD</td>
<td>CIS</td>
<td>53% (n=35)</td>
<td>20% (n=32)</td>
<td></td>
</tr>
<tr>
<td>Colgan 1988 [15]</td>
<td>FBD</td>
<td>CIS</td>
<td>57% (n=37)</td>
<td>6% (n=2)</td>
<td></td>
</tr>
<tr>
<td>Corey and Stanton 1990 [16]</td>
<td>IBS</td>
<td>CIS</td>
<td>48% (n=42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craig and Brown 1984 [17]</td>
<td>FBD</td>
<td>PSE</td>
<td>42% (n=79)</td>
<td>18% (n=56)</td>
<td>8% (n=135)</td>
</tr>
<tr>
<td>Ford 1987 [18]</td>
<td>IBS</td>
<td>PSE</td>
<td>54% (n=134)</td>
<td>12.5% (n=16)</td>
<td></td>
</tr>
<tr>
<td>Toner 1990 [19]</td>
<td>IBS</td>
<td>DIS</td>
<td>59% (n=44)</td>
<td>14% (n=19)</td>
<td></td>
</tr>
<tr>
<td>Blanchard 1990 [20]</td>
<td>IBS</td>
<td>DIS</td>
<td>56% (n=68)</td>
<td>25% (n=44)</td>
<td>18% (n=38)</td>
</tr>
</tbody>
</table>

chronic GI clinic attendees with persistent or refractory GI symptoms higher than that of anxiety (10%) [32]. These findings suggest that while symptoms of anxiety, in particular symptom-related worries and fears (and the underlying pathophysiological mechanisms), are closely related to IBS, the high comorbidity rate of depression in chronic GI clinic attendees is likely to be related to the independent, enhancing effect of depression on healthcare-seeking behavior [24,25]. Alternatively, the comorbidity of IBS and depression may occur in a genetically distinct subset of patients who are more refractory to standard IBS treatments. This subgroup may also have a higher prevalence of comorbid fibromyalgia, which is frequently associated with depression [33].

High degrees of somatization (e.g. reports of unexplained physical symptoms) have been observed in both depression and IBS [34,35]. North et al. suggested that the excess anxiety and depression associated with IBS may be predominantly a characteristic of a subgroup of patients with somatization disorder and hence a tendency to over-report physical and psychological symptoms of distress [35]. While such an explanation may pertain to somatization disorder as defined by the DSM-IV criteria, the frequent comorbidity of both IBS and depression with various syndromes of physical pain and discomfort is, in the authors’ opinion, better explained by emerging mechanisms of central pain amplification and their close relationship with brain circuits involved in the generation of mood and affect (see below).

Role of affective disorders in determining healthcare-seeking behavior
It is commonly assumed that psychological factors, including affective disorders and life stresses, are the primary predictors of healthcare-seeking behavior amongst individuals with IBS symptoms [36,37]. However, a population-based study performed in Australia revealed that neuroticism, psychological comorbidity, and a history of abuse did not explain the healthcare-seeking behavior of individuals with IBS symptoms [12]. In contrast, severity and duration of abdominal pain had statistically significant and independent effects on the probability of subjects with IBS symptoms ever having sought care for abdominal pain and discomfort. In a survey of several studies in which individuals with IBS symptoms who sought medical care for their symptoms were compared with those who did not, the severity of abdominal pain was found to be the most consistent distinguishing factor, while anxiety and depression had less influence [22]. Depression and anxiety have been found to be more prevalent in clinical populations of IBS sufferers than in non-consulting subjects with similar symptoms; however, in these two population-based studies [22], psychological factors did not predict healthcare-seeking behavior for IBS symptoms. While the higher prevalence rates of anxiety or depression in patients seeking healthcare are consistent with similar reports concerning users of medical services in general [24,25], these differences seem to lessen in the case of the IBS studies controlling for severity and duration of abdominal pain.

Pathophysiological mechanisms
The various aspects of IBS symptomatology can best be viewed as a dysregulation of the complex interplay between events occurring in the gut lumen (e.g. microflora), the mucosa, the enteric nervous system (ENS), and the central nervous system (CNS), leading to alterations in gut motility, secretion, and mucosal immune activation, visceral sensation, and possibly mood. In the following section, the authors will briefly address several factors that have been implicated in the pathophysiology of both IBS and disorders of mood and affect.

Role of life stresses and traumatic life events in IBS
Patients with IBS often report that stressful life events precede the onset or exacerbation of IBS symptoms. In a questionnaire-based study of 135 IBS patients and 654 controls, 73% of the patients and 54% of the control group reported that stress led to abdominal pain [38]. Stress was also found to correlate with the number of bowel symptoms, disability days, and physician visits [39]. A prospective study in IBS patients found that >90% of the variance in IBS symptoms over a 16-month period was accounted for by prolonged, threatening stressors [40]. Another recent study demonstrated that a greater number of patients who developed IBS-like symptoms following an acute enteric infection (“post-infectious IBS”) reported having experienced major stressful life events around the time of the infection [41]. One of the reasons for the greater susceptibility of IBS patients to certain types of environmental stressors may be related to altered emotional or arousal responses as a result of early life environment–gene interactions (Fig. 2) [42]. In addition, and possibly related to this limbic hyper-responsiveness, differences in cognitive functions, such as somatic threat appraisal, coping skills, and belief systems regarding the management of life stresses and symptoms, may contribute to the reported hyper-responsiveness to stress [37].

A history of major traumatic events, major losses (e.g. the loss of a parent), or other aversive life events during childhood is present more frequently in IBS patients than in healthy controls [43]. In addition to daily stressors, a history of severe emotional trauma such as physical and sexual abuse, especially when incurred during childhood, also appears to be associated with an increased risk of IBS [44–46]. It remains to be determined if genetic polymorphisms, such as the serotonin transporter gene-linked promoter region...
(5-HTTLPR) polymorphism, is an additional vulnerability factor that increases the risk of poor long-term outcomes following aversive early life events (Fig. 3) [47,48].

**Brain–gut interactions and 5-HT signaling**

Ninety-five percent of the body’s 5-HT is located in the GI tract, with the great majority being contained in ECCs interspersed within the gut epithelium [49]. In response to luminal stimuli (irritation, toxins, mechanical distortion), these cells release 5-HT in a paracrine fashion, activating 5-HT receptors on intrinsic (e.g. ENS) and extrinsic (primarily vagal) afferent nerves. In addition, 5-HT is released into the gut lumen where it may interact with enteric microorganisms [49]. Several recent studies have identified alterations in the gut-based 5-HT signaling system in IBS and in inflammatory bowel disease, even though no consensus has evolved regarding these findings and their relevance to GI symptoms in these disorders. Evidence of the involvement of alterations in the gut-based 5-HT signaling to vagal afferents in nausea and in eating disorders has been reported [50,51], and alterations in the 5-HT signaling within the ENS has been implicated in altered bowel function in IBS patients [52]. Based on the considerable evidence implicating the 5-HT signaling system in the regulation of the brain–gut axis and possibly IBS symptoms, IBS drug development has been focused on the development of 5-HT4R- and 5-HT3R-modulating drugs [49].

**Inter-relationship between central pain modulation mechanisms and regulation of mood and affect**

Afferent signals arising from the lumen of the gut are transmitted via various visceral afferent pathways (enteric, spinal, vagal) to the CNS [53–55]. Homeostatic reflexes, which generate appropriate gut responses to physiological as well as pathological visceral stimuli, occur at the level of the ENS, the spinal cord, and the pontomedullary nuclei and limbic regions [54]. Tonic and phasic vagal visceral afferent inputs, in part driven by ECC cell signals, may also play an important role in such diverse functions as modulation of emotion, pain, satiety, and immune response [56,57].

While the great majority of homeostatic afferent inputs from the gut (as well as other viscera) to the CNS are not consciously perceived [58], there are both peripheral and
central adaptive mechanisms that can result in the enhanced perception of visceral stimuli [59]. For example, acute tissue irritation and injury are typically associated with the sensitization of peripheral afferents, spinal circuits, and spino–bulbo–spinal circuits [60], which may result in a transient upregulation of afferent sensitivity, as demonstrated in preclinical models [61]. Similarly, various stressors have been shown to regulate visceral pain responses in animal models [62,63], and chronic life stressors have been associated with symptom severity in FGIDs [40]. There are multiple mechanisms within the brain–gut axis that can tonically or phasically up- or downregulate the sensitivity within visceral afferent pathways (influencing symptoms of pain and discomfort) [64], and the responsiveness of homeostatic reflexes (influencing bowel symptoms) [54].

Central pain facilitation mechanisms, driven by alterations in corticobulbar pontine pain modulation circuits, have been implicated in the enhanced perception of visceral as well as somatic events in IBS patients [65]. Recent evidence suggests that the hyper-responsiveness to visceral and emotional stimuli seen in IBS patients may be related to altered responses in pontine arousal circuits resulting in pain facilitation and ineffective engagement in corticobulbar pontine pain modulation circuits and in endogenous pain inhibition systems, leading to compromised pain inhibition [66]. Several similar alterations in the central processing of visceral and somatic signals from the body may also be involved in the chronic pain and discomfort characteristic of other functional pain disorders that are frequently comorbid with IBS, such as fibromyalgia, chronic back pain, chronic pelvic pain, or non-cardiac chest pain. It has been suggested that certain genetic polymorphisms related to general pain sensitivity may be shared by several of these syndromes [67].

**Emerging concept of neuroimmune interactions**

A new concept of altered CNS neuroimmune interactions has recently been proposed as a neurobiological substrate for chronic pain. Microglia and astrocytes (jointly referred to as “glia”) have been shown to be strong modulators of pain transmission and play an active role in the initiation and maintenance of hyperalgesia or allodynia in several animal models of chronic pain associated with inflammation or damage to peripheral tissues, peripheral nerves, spinal nerves, or the spinal cord [68]. Recent evidence from experimental animal studies indicates that CNS glia are also sensitive to environmental stressors. A number of studies have demonstrated immune activation within selected areas of the brain in response to experimental stressors in rats [69–71]. Although the nature of the pathways leading to CNS immune activation during stress remains unclear,
evidence suggests that microglia are the primary cellular source of increased pro-inflammatory cytokine levels in the brain [72]. Preliminary evidence from a rodent model of chronic stress-induced persistent visceral hyperalgesia suggests that spinal microglia activation plays an important role in the stress-induced changes [73]. Of particular interest in this context are recent reports suggesting a possible role for glia in the pathogenesis of depressive disorders [74]. Major stress has been proposed as a potential mechanism responsible for such changes [75]. In both chronic pain and depression, an increased level of pro-inflammatory cytokines in the periphery or within the CNS [reviewed in 74] has been observed, and may be associated with the prominent role of “vital exhaustion-type” symptoms in both IBS and depression patients. Taken together, the available data suggest that alterations in the neuroimmune interactions in the CNS may be considered a potential mechanism underlying the comorbidity of depression and IBS in a subset of patients, particularly in terms of enhanced pain sensitivity in both disorders.

Possible role of peripheral cytokines

There are several recent reports on altered plasma cytokine levels in IBS, including increased levels of interleukin-6 (IL-6) and IL-6 receptor [76], a lower ratio of IL-10 levels to IL-12 [77], and increased levels of IL-1β, IL-6, and tumor necrosis factor-α [78]. Even though it has been suggested that the origin of these circulating cytokines may be the gastrointestinal mucosa, there is currently no evidence to support this hypothesis. Elevated levels of pro-inflammatory plasma cytokines such as IL-6 have also been reported in depression, during somatic stress, and with intense exercise [79,80]. It is therefore plausible to assume that the reported increased plasma cytokine levels in IBS patients reflect the effects of chronic stress or are related to comorbid psychiatric conditions.

Animal models for functional pain disorders

The development of new therapeutic targets for functional pain disorders has relied predominantly on animal models that mimic certain clinical features of the conditions such as altered bowel habits (face validity), or show physiological abnormalities thought to be present in the syndrome, such as visceral hyperalgesia (construct validity). To date, several such animal models have been proposed [81]. The increased anxiety or heightened stress response observed in association with altered motility and pain perception in models of neonatal maternal separation supports the primary role of stress-induced CNS changes in IBS [82,83]. The fact that similar models are being used as preclinical models of depression further supports the hypothesis of shared CNS alterations in both IBS and depression. Other models using physical insults to the gut integrate the potential peripheral component in the process leading to central sensitization of pain perception [84]. Although each of these models has relatively good face and construct validity for functional bowel disorders, there are limitations to their predictive validity. This is illustrated by the failure to translate the drug efficacy seen in these rodent models into effective treatments for IBS symptoms.

Rationale for modulation of brain–gut interactions

Over the past decade, a remarkable convergence of research strategies pursued by different specialties (in particular those of pain, psychiatry, psychology, and stress neurobiology) has occurred, improving understanding of the interface between stress, pain, and emotion [reviewed in 85]. Rather than viewing each of these areas as mutually exclusive targets of research, the overlap of CNS circuits and neurotransmitter systems involved in the regulation and modulation of these processes and the resulting clinical disorders is fundamentally changing the perspective of national funding agencies and the pharmaceutical industry. The fact that drugs acting at the brain–gut axis make up an important aspect of every recent review published on the pharmacological treatment of IBS indicates the firm support in the field for this treatment approach [86].

Non-pharmacological treatments

Considerable evidence supports an important role for psychological treatments in IBS. In a meta-analysis of 17 high-quality studies, Lackner et al. reported an odds ratio of 12 (95% confidence interval 5.6–26) for efficacy, defined as a 50% reduction in symptoms [87]. Even though a wide range of psychotherapeutic approaches have been used to treat IBS patients, and solid evidence for the superiority of one over the other is currently not available, there is a general consensus that cognitive–behavioral approaches may be among the most effective of the non-pharmacological treatments. In particular, gut-directed hypnotherapy has been demonstrated to be superior to placebo in both adult and pediatric populations [88].

Pharmacological treatments

Antidepressants

Multiple central and peripheral mechanisms have been suggested as mediators of the beneficial effect of different classes of antidepressant drugs on IBS symptoms. Proposed central mechanisms include the treatment of comorbid depression, sleep restoration, analgesia, or antihyperalgesia, while proposed peripheral mechanisms include anticholinergic effects, normalization of GI transit, and peripheral anti-neuropathic effects. Tricyclic antidepressants (TCAs) have
been shown to decrease sensitivity to somatic pain and to improve sleep; therefore, they might also be particularly beneficial for FGID patients with associated extra-intestinal symptoms [89,90]. A detailed review of relevant studies and a suggested paradigm for their use has recently been reported [91].

**Tricyclic antidepressants**

TCAs are prescribed for a number of pain-related disorders, including neuropathic pain, migraine, and fibromyalgia [92–94], as well as FGIDs. With regard to their therapeutic effects on clinical pain, a primary beneficial response for neuropathic pain has been indicated [92].

Most published studies have shown that TCAs improve symptoms in FGID patients; however, the quality and design of these trials has been variable [95–99]. Of the three recent meta-analyses that have evaluated the possible therapeutic effects of TCAs on functional GI symptoms, the authors of two concluded that such treatments were beneficial [100,101], while the authors of the other concluded that they were not superior to placebo for the treatment of IBS [102]. Mayer et al. provide a detailed discussion of these studies [103]. In the largest randomized placebo-controlled trial to date, Drossman et al. evaluated the efficacy of a full dose of desipramine (150 mg/day) in 431 female patients with IBS and functional dyspepsia, followed for 12 weeks of therapy [104]. The study results demonstrated that treatment with desipramine was superior to placebo only in the per-protocol analysis (responder rate 73% vs. 49%, number needed to treat 5.2), and not in the intention-to-treat analysis. The beneficial effect of desipramine was seen primarily in diarrhea-predominant patients with moderate IBS symptom severity who had a history of abuse, but interestingly not of depression.

**Selective serotonin reuptake inhibitors**

It has long been hypothesized that selective serotonin reuptake inhibitors (SSRIs) may have a beneficial effect in IBS patients, mainly through treating comorbid depression and anxiety. However, preliminary results from several recent clinical trials suggest a possible direct effect on IBS symptoms. A recent double-blind, placebo-controlled study of the SSRI citalopram showed benefits in a number of IBS symptoms compared with placebo in a group of non-depressed patients [105]. After 6 weeks of therapy, patients treated with citalopram showed decreased abdominal pain and bloating, and increased overall well-being, though stool scores showed little change [105]. Other studies of the use of SSRIs for treating IBS have shown benefit, but have poorly differentiated the improvement of psychological symptoms from GI symptoms. In a study by Tabas et al., 81 IBS patients were randomized to either paroxetine or placebo. The paroxetine group showed greater improvements in global well-being (63% vs. 26%; p=0.01), but no difference in abdominal discomfort or bloating [106]. While the global improvement scores did not appear to be due to changes in depressive symptoms, anxiety symptoms significantly improved in the paroxetine group, possibly mediating the overall improvement. Another study comparing paroxetine with usual care for IBS patients reported improvement in the physical component of the Short Form-36 health-related quality-of-life score, but not in abdominal pain [107]. However, the study had a high discontinuation rate, with only 43 of the initial 86 patients completing the 12 weeks of therapy. In a randomized, placebo-controlled, 12-week trial of low-dose fluoxetine (20 mg/day) in 44 constipation-predominant IBS patients, a significant decrease in the presence of discomfort, bloating, hard stool, and decreased stool frequency was noted at 4 and 12 weeks [108]. However, the study authors did not report a global improvement outcome measure or whether the change in symptoms was associated with a psychological improvement.

Newer monoamine reuptake inhibitors, such as the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine, milnacipran, and venlafaxine, have been proposed as more effective treatments for chronic pain conditions associated with depression [109,110]. It is assumed that the combined effect of these drugs on descending serotonergic and noradrenergic pain inhibition systems (similar to the effect of TCAs) may be responsible for their effectiveness in the treatment of chronic functional pain conditions such as fibromyalgia [111] and painful diabetic neuropathy [112,113]. While there may be a theoretical advantage of these newer drugs over TCAs and SSRIs for the treatment of IBS symptoms, clinical evidence for such superiority is currently not available.

In summary, the hypothetical rationales for using centrally acting drugs with antidepressant and anxiolytic effects in the treatment of FGIDs are strong, and include the anxiolytic effect of these drugs on central mechanisms thought to play a role in IBS pathophysiology (hypervigilance, symptom-related anxiety, and increased stress-responsiveness), the potential antihyperalgesic effects of TCAs and SNRIs, and the therapeutic effects on mood. The use of low dose TCAs and full dose SSRIs in selected patients (or patient populations) appears promising, although individualized dosing and patient education is likely to be necessary to avoid side effects and to ensure treatment compliance. Similar to therapies for depression, the combination of antidepressants with cognitive–behavioral approaches may be superior to treatment with either modality alone. The reasons for the greater efficacy in certain subgroups of patients is
incompletely understood, but may be related to differences in underlying pathophysiology and possibly differences in genetic polymorphisms.

Emerging pharmacological treatments with potentially beneficial effects for both IBS and depression

Neurokinin receptor antagonists

The neurokinin family of neuropeptides includes substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), which bind with different degrees of specificity to their respective neurokinin receptors (NKR)s, NKR₁, NKR₂, and NKR₃. The widespread expression of SP in the body, the distribution of NKR throughout the autonomic nervous system (including the ENS) and the CNS, and the general role of the neurokinin signaling system as a modulatory rather than a primary transmission system, make the NKR a potentially interesting target for the pharmacological modulation of sensory and motor dysfunctions in FGIDs. Unfortunately, despite strong preclinical evidence, early evaluations of NKR antagonists for the treatment of acute and chronic somatic pain have been disappointing [114]. Similarly, studies evaluating the same class of compound for the treatment of depression have been equivocal, even though both preclinical and early clinical data were highly encouraging [115]. However, newer compounds have several advantages over the originally tested compounds, including better CNS penetration, optimization for the human receptor, and reduced interference with the cytochrome P450 system. In addition, less selective compounds with effects on more than one of the NKR may be superior to the highly selective agents. Thus, a re-evaluation of these treatment strategies for IBS is currently underway.

NKR, antagonists

NKR₁, antagonists are the preferred NKR subtype for SP, and their role in GI motility has been extensively described in preclinical studies [116]. In general, NKR₁ antagonism reduces GI motility in sensitized rodent models (inflammation, stress), but has little effect on motility under control conditions. The NKR₁ antagonist TAK-637 was found to reduce SP- or stress-induced exacerbation of colonic transit and defecation in gerbils [117]. The selective NKR, antagonists SR-140333 and MEN10930 were found to inhibit colonic propulsive activity induced by a NKR, agonist in vitro [118]. Similar to their effect on GI motility, NKR₁ antagonists have shown antihyperalgesic effects in several sensitization models in rabbits and rats with little effect on visceral pain sensitivity in control animals [83,119,120]. A central or spinal site of action has been proposed based on observations of enhanced visceral sensitivity to colonic or colorectal distension observed after stress exposure [83,119,120], or colonic inflammation [120], being attenuated by intracerebroventricular or spinal injection of NKR₁ antagonists.

Even though there has been extensive clinical trial experience with different NKR, antagonists in somatic pain [121], depression [122], and chemotherapy-induced nausea [123], the data supporting the possible use of NKR, antagonists in the treatment of IBS symptoms are limited. The only reported double-blind, placebo-controlled, randomized study revealed that a 7-day course of the NKR, antagonist ezlopitant (CI-11974) in 14 IBS patients reduced the emotional response to rectosigmoid distension and produced a trend toward decreased perception of rectal distension [124].

Evaluation of the NKR₂ antagonist zal坦net in two well-designed clinical trials in IBS patients did not provide any evidence for its effectiveness in treating symptoms of IBS [125], while antagonists aimed at NKR₃ and at multiple receptor combinations are currently underway.

CRF receptor antagonists

The discovery of new CRF-related peptides and CRF receptor (CRFR) subtypes, and the development of selective antagonists for CRFR subtype 1 (CRFR₁) and 2 (CRFR₂) have provided tremendous insights in understanding the mechanisms by which stress affects GI functions [126]. Convergent evidence from extensive preclinical studies has established the role of the brain CRF–CRFR₁ signaling system in mediating endocrine, autonomic, behavioral, and visceral responses to stress, suggesting that these receptors might be an ideal target in the context of functional bowel disorders [126]. Selective CRFR₁ antagonists (CP-154526, CRA-1000, NBI-35965, or NBI-27914) injected intracerebroventricularly or peripherally were found to blunt stress-related anxiety-like behavior, stress-induced visceral hyperalgesia, and stress-induced stimulation of colonic secretion and motility in rodents and monkeys [127–129]. In addition to its central effects, CRF, via the activation of CRFR₁ on myenteric neurons, plays an important role in colonic secretory and motor functions, as well as colonic permeability [130,131]. Furthermore, several CRFR, antagonists have demonstrated antidepressant-like efficacy in animals and a non-peptide CRFR, antagonist has been shown to reduce symptoms of major depression in an open-label clinical trial [132], supporting a possible role for CRFR₁ antagonists in the treatment of depression. A recent study from Sagami et al. reported an inhibitory effect on intravenous injection of the non-CNS-penetrable, non-selective CRFR antagonist α-helical CRF₉⁻₄₁ on enhanced motility induced by colonic distension and electrical stimulation of the rectal mucosa in diarrhea-predominant IBS patients [133]. Antagonism of peripheral CRFR₁, in the ENS has been proposed as a possible mechanism
for these effects. In contrast to the blood–brain barrier of the CNS, no such mechanism exists for the ENS. A significant reduction of abdominal pain and anxiety scores was also noted. Assuming that the peptide antagonist used in these studies does not cross the blood–brain barrier, the mechanism or mechanisms by which the anxiolytic and antihyperalgesic effects are mediated remain to be determined. One may speculate that the effect of the peripherally restricted α-helical CRF1-9-41, in these studies may be mediated by CRFR on vagal afferents indirectly modulating limbic activity, or its central effects via CRFR at the level of the circumventricular organ (unprotected by the blood–brain barrier). Alternatively, since stress can increase the permeability of the blood–brain barrier, the antagonist may circumvent the barrier. Alternatively, since stress can increase the permeability of the blood–brain barrier, the antagonist may gain access to the brain in patients with stress-sensitive disorders, such as IBS. Even though these initial observations need to be confirmed, the extensive preclinical evidence for the crucial role of the CRFR, in mediating the majority of behavioral, perceptual, and visceral alterations implicated in IBS pathophysiology are encouraging for the development of CRFR, antagonists for the treatment of IBS.

Conclusion

Considerable clinical, epidemiological, and neurobiological evidence supports the close association of IBS with disorders of mood and affect. While anxiety appears to be closely linked with IBS symptoms in the majority of patients, comorbidity of IBS with depression appears more common in patients with more severe symptoms, in patients with comorbidity with other functional disorders such as fibromyalgia, and in patients who have a greater resistance to IBS therapy. Novel compounds in development hold promise for treating both GI and psychiatric symptoms.

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References


Neurostimulation Therapies for Depression: Acute and Long-Term Outcomes

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Neurostimulation treatments in psychiatry, including electroconvulsive therapy (ECT), magnetic seizure therapy, transcranial magnetic stimulation, vagus nerve stimulation, and deep brain stimulation, represent an expanding class of therapeutic strategies for resistant forms of major depression. In contrast to neuropharmacology, neurostimulation is a physical intervention that utilizes the application of either an electrical current or a magnetic field to directly stimulate the brain or central nervous system. This article reviews currently available neurostimulation therapies, with a particular emphasis on data that address the durability of response. Further development and optimization of the efficacy and safety of these treatments are required, but as a therapeutic class there appears to be considerable potential for both ECT and newer neurostimulation techniques to benefit certain patients suffering from treatment-resistant depression. Depression: Mind and Body 2007;3(3):106–14.

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Major depression is common and debilitating, and standard antidepressant therapies are frequently ineffective at achieving remission in the majority of patients treated for the disorder; 50–60% of depressed patients do not adequately respond to antidepressant treatment [1]. A recently completed US National Institute of Mental Health-sponsored, multicenter clinical trial was designed to examine the relative effectiveness of serial antidepressant treatment interventions (STAR*D [Sequenced Treatment Alternatives to Relieve Depression]; www.star-d.org, last accessed in June 2007). In the large, broadly representative sample of depressed patients enrolled (n=3671), who were participating in a stepwise progression through multiple, serially administered, adequate antidepressant treatment trials, the cumulative remission rate was only 67% [2]. Non-pharmacological neurostimulation therapies may therefore offer new hope, especially for depressed patients who have failed to respond to standard psychotherapy and pharmacological therapies.

Neuromodulation interventions involve the use of direct electrical or magnetic stimulation to target central nervous system activity. Electroconvulsive therapy (ECT) is the oldest and most widely used neuromodulation technique. Vagus nerve stimulation (VNS) was approved by the US Food and Drug Administration (FDA) in 2005 as an adjunctive treatment for treatment-resistant major depression, and a device for the delivery of transcranial magnetic stimulation (TMS) as a treatment for depression is currently under FDA review. Other neurostimulation treatments for depression under development and investigation include magnetic seizure therapy (MST) and deep brain stimulation (DBS). In addition to a brief description of each treatment modality listed above, the acute and long-term outcomes associated with these neuromodulation therapies will be reviewed here.

Electroconvulsive therapy

ECT, considered the most effective treatment for severe forms of depression, has been in use since the 1930s, although a device manufactured for the delivery of ECT was approved by the FDA for treatment of depression as recently as 1979. In light of the importance currently associated with the regulatory process of evaluation and approval of new therapeutic drugs and devices, it is noteworthy that the efficacy and safety data typically required for approval of novel therapies today were not available or required when ECT was officially indicated for the treatment of depression. In addition to being considered the gold standard with regard to efficacy for treatment of severe depression, ECT has been used to treat various other severe psychiatric disorders, including mania, schizophrenia, and catatonic states [3].

ECT involves the unilateral or bilateral application of a brief electrical impulse directly to the scalp to induce
seizures. Some experts maintain that to be effective, an ECT stimulus must produce a tonic–clonic seizure movement pattern in addition to a characteristic tracing on a scalp electroencephalograph recording for ≥20 s [4]. Patients receive general anesthesia during modern ECT, and anesthesia-induced muscle relaxation prevents motor convulsions during the course of each session. A typical acute course of ECT consists of between six and 12 treatments at a frequency of two to three treatments per week.

Two recent meta-analyses, incorporating data from randomized controlled trials and observational studies, have confirmed the efficacy of ECT for depressive disorders [5,6]. In the first, ECT was found to be more effective than sham treatment in an analysis of six trials (n=256), as evidenced by a standardized effect size (SES) of −0.91 (95% confidence interval [CI] −1.27 to −0.54) [5]. Analysis of data from 18 trials (n=1144) suggested that ECT was significantly more effective than pharmacotherapy (SES −0.80, 95% CI −1.29 to −0.29) [5]. In addition, bilateral ECT was found to have greater efficacy than unipolar ECT (22 trials, n=1408; SES −0.32, 95% CI −0.46 to −0.19) [5]. The second meta-analysis, which included data from both randomized and non-randomized controlled trials published from 1956 to 2003, confirmed the superiority of ECT in comparisons with simulated ECT, placebo, antidepressants in general, tricyclic antidepressants, and monoamine oxidase inhibitors [6]. ECT tolerability and efficacy vary according to the specific treatment parameters and the patient sample used. Adjustable parameters include electrode placement, stimulus intensity, and the number and frequency of treatments. Current ECT devices enable manipulation of the electric stimulus itself, allowing for adjustment of pulse frequency, width, amplitude, and duration [7].

Sackeim and colleagues reported that the clinical efficacy of ECT is dependent on electrode placement (bilateral treatment being superior to unilateral) and stimulus intensity as a function of an individual’s seizure threshold (higher doses are superior to lower doses) [8]. Conversely, the absolute electrical dose was shown to be unrelated to clinical efficacy. A higher dose relative to seizure threshold and bilateral electrode placement appeared to be more effective at alleviating depressive symptoms, although these parameters were also associated with greater impairment of short-term cognitive function. This relationship is particularly notable in the elderly population receiving bifrontal ECT [9]. Although low-dose, right-sided unilateral ECT was shown to be the least effective type of ECT [8], preliminary results of a study by the same group suggest that further refinement of right-sided unilateral stimulation parameters, specifically the use of a stimulus pulse width of 0.1–0.3 ms and an electrical dose that adequately exceeds the seizure threshold, could produce a response equivalent to that achieved with standard bilateral ECT [10]. While awaiting a more systematic evaluation, the ultra-brief pulse dosing approach and other parameter adjustments, which optimize efficacy and limit side effects, hold promise for improving the acceptability of ECT with regard to cognitive impairment. It has recently been suggested that right-sided unilateral ECT at 250% of the seizure threshold was comparable with bilateral ECT at 150% of the motor threshold with regard to both side effects and clinical improvement [11].

While the efficacy results reported for ECT research protocols are impressive (in the 70–90% range), an analysis of treatment in community settings by Prudic and colleagues has produced ECT remission rates that are considerably lower than those achieved in clinical trials, ranging from 30–47% depending on the specific remission criteria applied [12]. In this naturalistic 6-month follow-up study, comorbid personality disorders, depressive episode chronicity, and schizoaffective disorder were associated with poorer outcomes. Among those who did achieve remission, 64% relapsed during follow-up despite continuation pharmacotherapy or ECT as dictated by treating psychiatrists.

Relapse rates as high as 84% have been reported within 6 months of initial ECT response in the absence of active treatment continuation, but this is reduced by the use of optimal antidepressant pharmacotherapy [13]. Naturalistic data provide additional support to the notion that a combination of maintenance ECT and antidepressant medication are superior to medication alone for reducing relapse rates [14]. A recent multicenter, randomized, 6-month trial that compared continuation ECT with pharmacotherapy following ECT-induced remission demonstrated no significant difference between the two treatments in relapse prevention, with both study arms demonstrating a relapse rate of >30% [15]. A naturalistic study examining outcomes 4–8 years after ECT in 26 patients reported an overall recurrence rate (i.e. a new episode requiring treatment) of 42.3% and determined that future recurrence was not associated with clinical outcome in the 6 months immediately following the initial ECT treatment [16].

Factors other than the high relapse rate limit the desirability of ECT. These include limited patient access because of the required hospital setting, cost, exposure to anesthesia, and risk of side effects, most notably amnesia [8]. As mentioned previously, immediate post-ECT side effects include short-term memory loss and cognitive impairment, specifically on selective attention and executive tasks [17,18]. In general, the extent and duration of longer-term cognitive side effects appear highly variable, and recent investigation has targeted various aspects of treatment that may have a potential effect on cognition [19].
Anterograde memory deficits have been shown to significantly improve within 1 week of the ECT procedure, and the administration of pulse-wave ECT appears to have lesser effects on attention and executive functions than sine-wave ECT [18]. Several studies have evaluated the prominence of ECT-induced short-term memory loss and cognitive impairment over time and found persistent or residual effects to be minimal. One research group found memory function returned to the level measured at (depressed) baseline 1 month after brief-pulse ECT, with a more substantial improvement in memory function relative to baseline seen at 6-month follow-up [20]. Another report of 6-month outcomes concluded that those ECT sessions produced superior clinical benefits to standard pharmacotherapy, including improvement in overall memory function relative to that at depressed baseline, especially when clinical benefits were marked [21]. A small naturalistic study of 10 ECT patients found evidence of slightly subnormal performance on working memory and verbal/visual episodic memory tasks over 2 years, but no severe persistent side effects of ECT or clinically significant signs of residual mood disorder [22].

Results of a large-scale, multicenter, prospective study examining the cognitive effects of ECT were recently published [19]. The findings confirm the link between persistent retrograde amnesia and bilateral application of ECT. In addition, sine-wave stimulation was associated with a pronounced slowing of reaction time, both immediately and in the 6 months following ECT. Advancing age, lower premorbid intellectual function, and female gender were associated with greater cognitive deficits [19].

Magnetic seizure therapy
MST is a novel, highly investigational neurostimulation technique combining facets of ECT and repetitive TMS (rTMS). The administration technique and principle of MST is borrowed from TMS; however, as with ECT, the goal of treatment is to produce a seizure. MST aims to combine the positive aspects of both therapies to produce a highly efficacious antidepressant treatment with few side effects [23].

MST uses a higher intensity, more frequent, and longer duration of stimulation than TMS in order to induce seizures similar to those of ECT. As with TMS, the magnetic field in MST passes through the skull unimpeded. This differs from ECT, where the skull shunts electricity away from the brain creating multidirectional spread of the stimulus and inducing a more generalized seizure activity. MST is therefore able to produce more focal activity and thus more localized seizures. Such activity may enable MST to maximize antidepressant efficacy while minimizing cognitive side effects.

Currently, only two clinical trials have evaluated MST in a preliminary fashion. In a randomized, treatment crossover, double-blind trial, Lisanby and colleagues examined ECT and MST in a sample of 10 patients with depression who had been referred for ECT [23]. Each patient was treated with two MST and two ECT sessions. Placement of electrodes during ECT was clinically determined, with nine patients receiving right unilateral ECT and one receiving bilateral ECT. MST coils were optimally positioned to activate the motor cortex. The first treatment session of each technique was conducted at the seizure threshold, while the second consisted of suprathreshold stimulation. While efficacy data were not obtained, the relative tolerability of each stimulation technique was evaluated using a side-effect rating scale and neuropsychological testing. MST was successful in inducing tonic–clonic seizures in all patients and was significantly better tolerated than ECT, as evidenced by both decreased physical side effects and increased scores on cognitive measures, including disorientation recovery, attention, and certain tests of retrograde and anterograde amnesia. In particular, MST tended to be superior to ECT in those cognitive domains thought to be subserved by medical temporal structures.

A second study examined more extended treatment with MST in comparison with ECT [24]. Matched experimental groups of 10 patients each received 10–12 treatments of bilateral ECT or MST over the motor cortex during the course of 3–4 weeks. Although both groups demonstrated a significant decrease in depressive symptomatology from baseline, ECT resulted in significantly lower depression ratings following acute treatment. However, patients receiving MST demonstrated a faster recovery of cognitive function and, based on remnants of muscle paralysis after the return of cognitive function, a diminished need for the administration of muscle relaxants.

While positive outcomes of two 2003 case reports are auspicious predictors for therapeutic success [7,25], conclusions regarding the short- and long-term efficacy and relative merits of MST await additional clinical trials data. Although research suggests that MST may produce fewer side effects than ECT, controlled efficacy data are not yet available. Development of MST treatment, including improvements to the device used for its delivery and refinement of the stimulation parameters, is currently underway [26].

Transcranial magnetic stimulation
During TMS, a small, insulated electromagnetic coil is placed on the scalp. A bank of capacitors is then rapidly discharged into the coil, which converts the electrical activity into a pulsed magnetic field that passes through the cranium with minimal impedence. The magnetic field induces an electrical
field in the underlying cerebral cortex, based on the countercurrent principle [27,28]. Upon delivery of TMS to the targeted area, and if the induced electrical field is of sufficient intensity, the cortical neurons depolarize and action potentials are generated. The currently employed technology generates a magnetic field of approximately 1.5 Tesla (comparable to that in standard magnetic resonance imaging (MRI)), which penetrates to approximately 3 cm beneath the coil surface [29]. The pulsing frequency of the field and the excitatory or inhibitory function of the activated underlying neurons together determine whether the ultimate effects on neural circuitry are excitatory or inhibitory. In general terms, frequencies of ≤1 Hz (slow TMS) are inhibitory and frequencies >1 Hz (fast TMS) are excitatory [30–32]. The pulses administered can be single, paired, or in series (also called a train, which can vary in its duration). When TMS is delivered in a series of pulses, this is generally termed repetitive TMS (rTMS). Single and paired pulse TMS are more frequently used for neurodiagnostic purposes, whereas rTMS is believed to have therapeutic potential in psychiatric disorders.

Unlike ECT, which produces a widespread current distribution, the rTMS device is able to induce currents in localized areas [33]. While several target sites have been investigated for the treatment of major depression, the majority of studies that have shown efficacy have delivered stimulation to the left dorsolateral prefrontal cortex (DLPFC). An imaging study of 1-Hz TMS interspersed with functional MRI showed that direct rTMS of the left DLPFC indirectly activated deeper structures, including the insula, putamen, hippocampus, and thalamus, via frontal–subcortical neuronal circuits [34].

The minimum amount of energy required to activate the motor strip of a particular individual is called the motor threshold (MT), and is determined by titrating the amount of energy from the rTMS device (expressed as a percentage of the device’s available output) until a visible movement of the contralateral thumb is reliably produced following single pulses of TMS. Determination of the MT on the left motor cortex guides the dosing for the power of treatment delivered (expressed as a percentage of MT), usually in the 80–120% range. Other techniques are available to identify the rTMS target site. One commonly used method involves a 5 cm anterior movement of the coil in a parasagittal plane from the site of MT determination to the scalp overlying the DLPFC.

rTMS is a non-invasive neurostimulation procedure, which does not require anesthesia and can be performed on an outpatient basis. Usually, only a single session is conducted per treatment-day, with five sessions per treatment-week given for acute treatment. In clinical trials, the total number of treatment sessions ranged from 10–20 in 3–4 weeks in the earlier studies [35], with newer studies expanding the duration of treatment to 6 weeks [36]. Patients are not sedated during the rTMS treatment and can normally leave immediately afterwards without a recovery period. Devices that deliver rTMS are approved for the treatment of depression in Canada and Israel, and one is currently under FDA review for depression treatment in the US (Neuronetics, Malvern, PA, USA; personal communication).

The safety profile of rTMS is fairly benign, particularly when compared with other options for neurostimulation. Although there is a risk of inducing a motor seizure, this is minimized with correct use of the technique. Headache or discomfort at the stimulation site on the scalp is fairly common, but relatively insignificant compared with that associated with ECT. In older devices, the high-frequency clicking noise that occurred during coil discharge occasionally resulted in mild high-frequency hearing loss [37], but this issue has been addressed in the development of a newer version of the device (Neuronetics; personal communication). Nevertheless, earplugs are typically worn during TMS therapy to minimize any such occurrence.

Although rTMS was first suggested as a possible treatment for depression in 1987 [38], the initial studies in patients with major depression were essentially case reports or series [39,40]. It was not until 1996 that TMS was first systematically examined for the treatment of this disorder [41]. Over the last 10 years, there have been approximately 30 single-center controlled trials of rTMS in the treatment of depression, most of which have included both bipolar and unipolar depressed patients. Early studies were limited by safety concerns posed by the FDA and other regulatory bodies and, in addition, the short courses of treatment (usually 1–2 weeks). Perhaps as a consequence of this, some trials were negative while others yielded statistically significant but clinically modest results. An analysis of treatment parameters associated with optimal rTMS outcomes in patients with depression revealed that longer courses (>10 days of rTMS sessions compared with ≤10 days), higher-intensity MTs (100–110% vs. 80–90%), and a greater number of pulses per day (1200–1600 pulses vs. 800–1000 pulses) were superior [42]. Using optimized dosing parameters, response rates to rTMS in the order of 50% have been seen for treatment-resistant depressed patients [43], whereas response rates of 30% were observed in studies that used the suboptimal dosing parameters [42,44].

Recent rTMS trials have more systematically evaluated the relative merits of various stimulation parameters. Fitzgerald and colleagues found no significant difference between rTMS administered at frequencies of 1 and 2 Hz to the right-sided DLPFC in an initial 2-week treatment phase of adjunctive rTMS in treatment-resistant depressed patients on antidepressant pharmacotherapy [43]. In a subsequent
extension phase for initial non-responders, higher frequency rTMS (5 or 10 Hz) applied to the left-sided DLPFC produced decreases in depressive symptoms, but there was no evidence of superiority with 10 Hz over 5 Hz on the left side [43].

The same group investigated the combined application of fast rTMS over the left DLPFC and slow rTMS over the right DLPFC, with the modalities administered in a sequential fashion, compared with a sham control condition of similar duration in a sample of treatment-resistant depressed patients (n=50) [36]. Those who received active rTMS over a period of up to 6 weeks had response rates of 44–52% (depending on the rating scale used) and remission rates of 36–40%.

In another recent study of rTMS sequenced in a combination treatment fashion, high-frequency stimulation (20 Hz) to the left PFC and low-frequency stimulation (1 Hz) to the right PFC resulted in significantly greater decreases in depressive symptomatology than did sham control treatment (p=0.048) [45]. No additional clinical advantages were obtained by focusing rTMS on areas identified by single-photon emission tomography as showing high versus low levels of functional activity.

The results of a large, multicenter, double-blind, monotherapy rTMS study that randomized 325 medication-free patients with major depression have recently been published [46]. rTMS was delivered five times per week for 4–6 weeks at 10 pulses/s, 120% of MT, 3000 pulses/session. All patients met the diagnostic criteria for major depressive disorder (MDD) and were moderately treatment-resistant, having failed to respond to at least one, but not more than four, antidepressants during the current episode. In the evaluable sample (n=301), active rTMS was superior to sham treatment on the primary outcome measure at week 4, and on the secondary outcome measure at weeks 4 and 6. The initial blinded phase of this study resulted in a 24.5% response rate for rTMS compared with 13.7% for sham. Comparison of SEs for these results (0.55) with those of currently marketed antidepressants (0.49) present a favorable profile for rTMS [29].

At the end of this acute-phase trial, patients who did not respond to stimulation, regardless of their treatment condition, were invited to cross over to an open-label rTMS trial consisting of a similarly designed 6-week phase. Patients remained blinded to their original treatment condition in order that additional data for evaluating the efficacy of acute rTMS could be generated (i.e. in patients originally assigned to sham stimulation) in concert with data on late rTMS responders (i.e. in patients initially assigned to active treatment who did not respond). A third phase of the study allowed for the transition of rTMS into a 24-week continuation phase, with antidepressants available for optional pharmacotherapy in the event of symptom worsening. While the results of the crossover and continuation phases await peer-reviewed publication, preliminary results suggest that the outcomes for those who crossed to the open-label study are comparable with those observed in the blinded acute phase (42–43% response and 20–27% remission rates, depending on the scale used) [47]. Maintenance of the beneficial effects of rTMS is suggested from preliminary 24-week data showing lower relapse rates among those who received active (8%) rather than sham (15%) treatment [47]. Safety data confirmed that common side effects, such as application site pain, muscle twitching, toothache, and discomfort in the facial/eye area, were mild-to-moderate and rapidly accommodated by the patient.

There are limited data on long-term outcomes and maintenance therapy with rTMS. One report, describing moderate-to-marked benefits achieved with maintenance rTMS in a cohort of 10 patients followed to 6 years indicates that rTMS may be an option for the long-term management of depressive symptomatology [48]. Side effects presenting during rTMS treatments over the course of this period were few and included occasional headache, dizziness, and jaw tremor in one session, and ear and sinus pain during a session in a patient with a sinus infection. Importantly, no patients reported serious adverse effects over the course of treatment (up to 6 years, depending on the patient). Preliminary data from the continuation phase study suggest that the addition of rTMS as an augmenting agent to ongoing antidepressant pharmacotherapy did not alter the safety profile seen with rTMS monotherapy [47].

The literature presents conflicting evidence concerning the relative benefit of rTMS compared with ECT. One study demonstrated similarly low response and remission rates for both rTMS (50% and 10%, respectively) and ECT (40% and 20%, respectively) in a medication-free, non-psychotic sample of patients with refractory depression [49]. A further comparison of a 15-day course of adjunctive rTMS with a standard clinical course of adjunctive ECT in a sample of depressed patients maintained on treatment as usual demonstrated the superiority of ECT over rTMS immediately following treatment [50]. Superior benefits in secondary outcome measures were maintained at 6-month follow-up. It is likely that patient selection factors (e.g. severity of symptoms, melancholic subtype, psychotic features, or degree of resistance to prior antidepressant therapies) will ultimately prove to be important in determining the relative efficacies of rTMS and ECT in a conceptual algorithm for the treatment of depression with neurostimulation.

Further research into rTMS is needed to define the long-term efficacy, optimal treatment parameters (e.g. coil positioning and stimulus frequency and intensity), and potential for use in other psychiatric disorders. Experts in this
field have emphasized the importance of thoughtful patient selection and have begun to identify predictors of response [42,51,52]. Given that the risks and inconvenience associated with the procedure are minimal, rTMS will likely prove a critical focus for future research.

Vagus nerve stimulation

VNS has been approved by the FDA for the treatment of pharmacoresistant epilepsy since 1997. Mood elevations observed in patients with epilepsy prompted the investigation of VNS as a treatment for depression; subsequent data resulted in the FDA approval of VNS therapy for depression in July 2005. VNS therapy consists of repetitive, cyclical stimulation applied to the vagus nerve (cranial nerve X). This indirect brain stimulation is thought to improve mood via ascending projections through the nucleus tractus solitarius to the parabrachial nucleus and the locus coeruleus. This is the site of many norepinephrine-containing neurons that have important connections to the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic regions linked to mood and anxiety regulation [41]. A large body of preclinical [53] and clinical research, including neuroimaging studies [54], has provided evidence of VNS-associated regional brain effects, but a putative antidepressant mechanism of action remains obscure [55].

VNS surgery is considered a procedure of low complexity and is typically performed in an outpatient surgical setting under general anesthesia. A pulse generator is implanted subcutaneously into the left wall of the chest and is connected to bipolar electrodes, which are attached to the left vagus nerve within the neck. After a post-surgical recovery period, typically of 2 weeks in the US, the device is turned on and stimulation is titrated to optimal treatment levels. Device “dosing” – including selection of stimulus intensity, duration, and off-interval – is non-invasive and adjusted by an external telemetric wand. A typical programming cycle consists of 30 s of stimulation followed by a 5-min off-period.

The safety of VNS is well established from its use in the treatment of epilepsy. In total, >40 000 patients have been implanted with the VNS device worldwide since the 1990s (Cyberonics, Houston, TX, USA; personal communication). The side effects of VNS are generally mild and are associated with stimulation (i.e. the “on” phase of the cycle). Voice alteration, dyspnea, and neck pain were the most frequently reported adverse events in a long-term follow-up study of VNS in patients with depression [56]. Adjustments in stimulation pulse width and frequency can also be performed to manage side effects and optimize therapy [57].

In an open-label pilot study, 60 patients with treatment-resistant major depressive episodes who had not responded to at least two trials of medication from different antidepressant classes received 12 weeks of adjunctive VNS while continuing on stable medication regimens [58]. Response rates ranged from 31–37%, depending on the scale used. The most common side effect was voice alteration or hoarseness, which was generally mild and related to output current intensity. VNS appeared to be most effective in patients with low-to-moderate, but not extreme, antidepressant resistance. A naturalistic follow-up study was conducted to determine whether the initial promising effects were sustained in a subgroup (n=30) following exit from the 3-month acute study [59]. At 1-year follow-up, response rates for the subgroup were sustained (40–46%) and remission rates significantly increased (17–29%), although psychotropic medications and VNS stimulus parameters varied during the follow-up interval.

Follow-up of the 59 patients from the original cohort who completed the study and who continued with adjunctive VNS demonstrated a response rate of 44% at 1-year, which was largely sustained (42%) after 2 years of active treatment [60]. Remission rates demonstrated a similar pattern, rising to 27% at 1-year follow-up and to 22% after 2 years of stimulation.

A large (n=235), randomized, sham-controlled, multicenter study of adjunctive VNS did not find a significant difference in acute-phase response between active and sham groups (15% and 10%, respectively) at the 12-week endpoint [61]. However, follow-up of this cohort over the subsequent year suggested a cumulative beneficial effect of treatment over time [56]. The initial active group therefore continued with treatment for another 9 months, while the sham group crossed over to receive 12 months of VNS. Participants received antidepressant pharmacotherapy and VNS, both of which could be adjusted. Response rates of 27–34% and a remission rate of 15.8% were observed. To better understand the long-term effects of VNS combined with treatment-as-usual (TAU), 12-month VNS+TAU outcomes (n=205) were compared with those of a similar group of patients with treatment-resistant depression (TAU; n=124) in a non-randomized study [62]. Repeated-measures linear regression was performed to compare the VNS+TAU group (monthly data) with the TAU group (quarterly data) according to scores on a self-report depression symptom scale. Adjunctive VNS was associated with greater improvement per month than TAU across 12 months (p<0.001), and response rates were 27% for VNS+TAU and 13% for TAU (p<0.011), supporting the finding of greater antidepressant benefit in VNS patients [62]. A 24-month study of patients treated with VNS therapy presented at the 2006 American Psychiatric Association annual conference concluded that patients with carefully defined treatment-resistant depression...
who received 24 months of VNS therapy had a decline in suicide attempts, suicidal ideation, and hospitalizations for worsening depression [63]. Recently published longer-term data indicate that patients identified as early (i.e. by 3 months) and late (i.e. by 12 months) responders maintained their response at a rate of 76.7% and 65%, respectively, at 24-month follow-up assessment [64].

**Deep brain stimulation**

DBS is an FDA-approved treatment for dystonia, essential tremor, and tremor in Parkinson’s disease, but remains highly exploratory for the treatment of depression and other psychiatric disorders. The relatively high risk associated with the required neurosurgical procedure means that this treatment modality is reserved for individuals with the most severe and treatment refractory disorders. Pilot studies of DBS for depression have included only patients who have failed multiple antidepressant treatment courses over several modalities, including ECT, evidence-based psychotherapy, and antidepressant medications in a variety of classes.

Surgery to implant the DBS device occurs in two phases. First, implantation of the electrodes through burr holes in the skull is performed with the patient under localized anesthesia. Placement of the electrodes into the targeted subcortical areas is guided by a stereotactic frame and MRI. Following implantation and successful testing, the electrodes are connected via lead wires tunneled subdermally under the scalp, neck, and chest wall areas to pacemaker-like pulse generators. This procedure is performed while the patient is under general anesthesia. As with VNS, adjustment of DBS stimulation parameters is performed via a computer-controlled telemetric wand.

Few studies have evaluated DBS as a treatment for depression, and as such only limited data have been published. Case reports describe improvements in mood in patients receiving DBS for treatment-resistant MDD, tardive dyskinesia, and most prominently, obsessive–compulsive disorder (OCD) [65–68]. Greenberg et al. presented preliminary findings suggesting efficacy of DBS on the ventral portion of the anterior limb of the internal capsule and the adjacent dorsal ventral striatum in a pilot study of five depressed patients over the course of 3 months [69]. Target areas for depression were defined based on observations of consistent improvement of comorbid depressive symptoms in patients with treatment-resistant OCD when treated with DBS of the ventral internal capsule [70]. During the initial acute-phase pilot study, all five patients demonstrated an improvement in depressive symptoms, with three of the five patients showing a 50% acute response and the remaining two patients achieving 23% and 17% reductions in depression score. Symptom scores were reduced significantly from baseline, and a corresponding increase was seen in ratings of social and occupational function. The five patients were successfully continued with DBS in an open-label fashion following a 3-month blinded period, and additional patients were enrolled in the pilot study at a second site. Preliminary data describing 1-year outcomes for the expanded group (n=11) of pilot study patients show response and remission rates of 56% and 33%, respectively [71].

A second DBS research group led by Dr Mayberg has examined DBS targeting the subgenual cingulate region in six patients with treatment-resistant major depressive episodes [72]. By 2 months, five of the six patients met the response threshold, and this was maintained in four of the five responders at the 6-month follow-up. Positron emission tomography scans at 3 and 6 months demonstrated normalized blood flow in the subgenual cingulate (decrease from baseline) and prefrontal areas (increase from baseline) in a subset of responders [72]. Results from an expanded sample of patients receiving DBS at this target and longer-term outcome data for this group have not yet been published.

DBS to the nucleus accumbens has recently been used to target anhedonia in a pilot study of three patients with treatment-resistant depression. Stimulation was delivered in a double-blind manner. In all three patients, clinical ratings of depression improved when the stimulation was active, beginning with the titration period and continuing through 1 week of active stimulation. Conversely, symptom ratings worsened when the stimulation was turned off. In this small group of patients, the results of DBS were immediately observable and offer further support for the use of DBS targeting the nucleus accumbens [68].

Several limitations of DBS therapy are apparent, even assuming further proof of its safety and efficacy for the relief of depressive symptoms. The risks from neurosurgery are high and include intracranial hemorrhage, edema, infection, and death [73]. An intraoperative seizure has been observed [69]. Hardware malfunctions are not unusual, and batteries typically require replacement every 1–3 years [73]. As in VNS, implantation of the generators into the chest wall can be somewhat disfiguring, depending on the location of the pulse generators and individual body habits. Transient side effects of DBS may include dose-dependent light-headedness, insomnia, and psychomotor changes; however, persistent side effects are unusual. Transient hypomania resulting from changes in stimulation parameters has been reported [69,74]. While data regarding DBS outcomes for the treatment of depression beyond 1 year are not yet available, the report describing 3-year outcomes in 10 patients receiving DBS for OCD suggests no cumulative side effects of treatment. Cognitive assessments have revealed no decline over the course of the DBS treatment period and
improvement in some areas of cognitive function, such as prose recall. Overall, these results demonstrate a fairly benign profile associated with long-term DBS of the ventral internal capsule [74], but the small numbers of patients enrolled in these pilot studies means that conclusions about longer term efficacy and safety cannot yet be drawn.

Conclusion

Neurostimulation therapies hold considerable promise for the treatment of depression, yet a number of issues, such as adverse effects, commercial availability, cost, insurance reimbursement, delivery setting, and strength of available data on efficacy, limit their current use. Refinements in the device technology and discoveries related to optimization of targets and stimulation parameters are likely to continue to inform development and enhance the appeal of this treatment modality during the next decade.

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References


Perinatal Depression: A Review

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Mental illness, a commonly encountered complication in the perinatal period, is filled with questions and controversies regarding its treatment. Many women refuse medication due to the possible risks to the fetus or child. Evidence of success with psychotherapy in this population is limited; however, leaving depression untreated has also been shown to have negative consequences for both the mother and her child. Early identification and treatment of perinatal depression and anxiety disorders is therefore of key importance. This report aims to promote timely identification of this under-recognized illness, highlighting the importance of screening and treatment methods. Depression: Mind and Body 2007;3(3):115–21.

Pregnancy is often considered a time of joy and happiness in a woman’s life, and a period of protection against mental illness. Although this remains true for most women, there are others for whom pregnancy can actually trigger a serious psychiatric illness, including mood and anxiety disorders. Rates of depression are significantly increased in pregnancy, particularly in the second and third trimesters [1–4]. It is unclear why the incidence is greater but it appears that there is a predictable relapse in late pregnancy [5], highlighting the need for early screening [6]. Studies have shown that 12.8% of women experience major depressive disorder (MDD) during pregnancy [3]. These findings are consistent with a recent study in British Columbia (BC), Canada, in which rates of depression in pregnancy were reported to be 13–15% in 1998–2001, and had increased to 17% in 2003–2004 [7].

It is widely acknowledged that the post partum period is a time of increased susceptibility to MDD, with a prevalence rate of 13% [8], and an increased risk of hospitalization [1,9]. Post partum depression, which has recently received increased attention due to celebrity Brooke Shields’ highly publicized personal experiences, often has its onset during pregnancy [10]. Josefsson reports that 45% of post partum depression has onset during gestation [2], a concept that has been hypothesized since the 1980s [11].

Antenatal depression is continually under-recognized and under-treated [12]. Diagnosis is often overlooked as the symptoms of depression and signs of pregnancy are closely linked. Awareness of antenatal depression is increasing as a result of its comorbidity with other perinatal anxiety disorders such as panic disorder, generalized anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder. Clinical observation shows that women with anxiety disorders often seek help earlier from their healthcare providers.

This review of perinatal, unipolar, non-psychotic depression will focus on the prevalence, risk factors, diagnosis, screening, and consequences of the condition for mother and child, as well as the current controversies and clinical realities in treatment practices.

Prevalence
Data from around the world have shown that women are twice as likely to develop depression than men, with the first onset frequently occurring in the childbearing years [13]. Pregnancy and the post partum period, along with miscarriage, infertility, and fetal death, are times when a woman’s mental health may be further challenged [13].

The DSM-IV-TR unfortunately does not address antenatal depression but, despite this omission, a recent meta-analysis has found the prevalence of depressive symptoms during the first, second, and third trimesters of pregnancy to be 7.4%, 12.8%, and 12.0%, respectively [3].

Risk factors
A variety of risk factors influence perinatal depression. Biological risk factors include a prior history of either MDD or post partum depression. It has been demonstrated that women with a prior episode of post partum depression are at a 30–50% risk of relapse in future pregnancies [13]. Psychiatric illness in family members, particularly first-degree relatives, is another significant risk factor [14–19]. First-degree relatives of patients with depression are 1.5–3 times
more likely to develop depression than the general population [17].

Another major risk factor is the discontinuation of antidepressant medications; patients who choose to discontinue their antidepressant medication during pregnancy significantly increase their risk of relapse when compared with those who remain on medication. A recent prospective study of 201 women with MDD found that 68% of the women who discontinued their medication relapsed; interestingly, 26% of women who remained on their medication also relapsed. [5]. Significant medical or obstetrical problems are also associated with depression rates in pregnancy [20–23].

A number of psychosocial risk factors contribute to perinatal depression. These include the lack of partner, family, or social support, stressful life events, abuse, cultural factors, socioeconomic status, and unplanned pregnancy [24,25]. Pregnant adolescents are at a higher risk of depression, and adolescents who are already depressed are at a high risk of becoming pregnant [26]. Indicators of lower socioeconomic status such as unemployment, lack of education, and low income are all risk factors in mental illness, particularly depression [24].

**Diagnosis**

The DSM-IV-TR does not have a separate classification for antenatal depression; however, there is a post partum-onset specifier that is limited to an onset of depression within 4 weeks of childbirth [27]. Clinically, a diagnosis within the first year of delivery is considered post partum depression. Diagnosis of depression in pregnancy is difficult for the caregiver as both these conditions have many symptoms in common, such as sleep and appetite disturbance, weight change, lack of energy, and lability of mood. One study found that only 26% of known cases of antenatal depression were identified during prenatal healthcare visits, with only 2% of these patients being referred for treatment [12].

**Screening**

Given the increased frequency of visits to healthcare providers during the prenatal period, there is ample opportunity to initiate a depression screening process [28–31]. Ideally and when feasible, screening for depression should occur early and continue throughout pregnancy, particularly when patients have a prior history of the condition. The Edinburgh Postnatal Depression Scale (EPDS) is the best-studied screening tool for assessing both antenatal and post partum depression and is recommended between 28 and 32 weeks of gestation [32,33]. The EPDS rates depressive symptoms from the previous 7-day period with higher scores being indicative of more intense symptoms. It consists of a 10-item self-report questionnaire, each question scored from 0–3 resulting in total scores ranging from 0–30; scores of ≥13 identify the most severely depressed women [34]. The EPDS is easy to read, administer, and implement. A 3-year study of women in Australia found that 85% of the participants experienced no discomfort with the EPDS, and 93% found the survey easy to complete [29]. In addition, researchers noted that discomfort with the EPDS was significantly related to an EPDS score of ≥13.

In BC, Canada, the BC Reproductive Mental Health Program and the Ministry of Mental Health and Addictions recently developed a Perinatal Depression Framework that includes mandatory screening of perinatal women with the EPDS administered between 26 and 32 weeks of gestation and 6 to 8 weeks post partum [6].

**Consequences of untreated antenatal depression**

Undetected and untreated antenatal depression has various consequences for the mother, fetus, infant, and child. Maternal complications include poor prenatal care, risk of medical/obstetrical care, exacerbation of psychiatric illness through the post partum period, self-medication or substance abuse, impaired bonding, and suicide [35–37]. Suicide has, in fact, been identified as one of the three leading causes of maternal death [22,35]. A retrospective study in California, USA, showed an elevated suicide attempt rate in pregnant women compared with age-matched, non-pregnant controls [22]. Risk factors for these attempts included young age, low socioeconomic status, multiparity, and a history of substance abuse.

Antenatal depression has been associated with preterm delivery and low birth weight [20,23,38–40]. When left untreated, maternal depression can result in infants with lower APGAR (Activity, Pulse, Grimace, Appearance, and Respiration) scores, small gestational age, and smaller head circumference [20,39,40]. Accompanying anxiety in pregnancy has been shown to result in neonatal complications such as lowered dopamine and serotonin levels, increased uterine artery resistance, greater right frontal electroencephalogram activation, and increased cortisol levels relating to lower birth weight [20,41–46]. Maternal anxiety has been associated with fetal movement and distress, as evidenced by fetal heart rate variability and sleep–wake cycles [42,44,46].

The Avon Longitudinal Study of Parents and Children demonstrated negative long-term neurobehavioral outcomes in offspring exposed to antenatal anxiety [47,48]. This sample showed that girls were affected by maternal anxiety at both 18 and 32 weeks gestation, while boys were only affected by maternal anxiety at 32 weeks gestation. These gender differences were noted at both 4 and 6 years of age.

In a study examining internalizing behaviors in 4-year-olds after in utero psychotropic medication exposure,
researchers found no significant differences between exposed and non-exposed groups [41]. These results suggest that current maternal mood is a strong predictor of a child’s internalizing behaviors. A further investigation examining the externalizing behaviors of the same 4-year-olds found these behaviors correlated with maternal depression and anxiety [49]. These results again confirm that current maternal anxiety and depression has an impact on their child’s externalizing behaviors [41,49].

**Non-pharmacological treatments for perinatal mood and anxiety disorders**

**Psychotherapy**

*Cognitive–behavioral therapy*

Cognitive–behavioral therapy (CBT) has been reported to be beneficial in the treatment of depression, anxiety, and eating disorders, with a success rate of 52–97% [50]. Although no studies have been published examining the efficacy of CBT in treating depression during pregnancy, the use of this type of therapy in women with post partum depression has been documented [51–53].

*Interpersonal therapy*

In pregnant women for whom role transition is a major issue, a study of 13 patients, which served as a pilot for a larger study, found interpersonal therapy (IPT) to reduce depressive symptoms with no post partum relapse [54]. A larger study of 38 women compared parenting education and IPT in the treatment of antenatal depression, and reported that patients receiving IPT experienced significantly greater improvements [55].

**Biological Treatments**

*Light therapy*

The use of bright-light therapy in the treatment of antenatal depression has shown promising results. Depressed pregnant women treated for 3–5 weeks with bright-light therapy experienced noteworthy improvements in their symptoms in one study [56]. Another trial that compared a 7000-lux treatment group with a 500-lux control group found a significant improvement in the 7000-lux group at 10 weeks [57]. Studies have also been published examining the successful use of light therapy for treating post partum depression [58].

*Other adjunctive therapies*

Exercise has been shown to be effective in improving both mood and anxiety symptoms throughout the three trimesters of pregnancy [59], while infant massage has been found to benefit mother–infant interaction as it encourages mothers to look at and understand their babies [60,61]. A small, controlled study found that while EPDS scores improved in mothers participating in a support group, the improvement was significantly greater in those also attending a massage group [60]. St John’s Wort has been effective in treating depression; however, no data are available at present that investigate its efficacy in women with antenatal depression [62]. Notably, in nursing women, St John’s Wort was found to be at detectable levels in the infants’ plasma [63].

So far, only one study has shown acupuncture to decrease depressive symptoms in pregnant women; a sustained effect was seen until 10 weeks post partum [64].

**Pharmacological treatments for perinatal mood and anxiety disorders**

Despite all of the recently published concerns, antidepressant medications remain the first-line treatment for pregnant or lactating women with moderate-to-severe relapsing mood and anxiety disorders. Studies have continually shown that discontinuing antidepressant medication, either prior to or during pregnancy, can lead to relapse of symptoms [5,65]. Although the secretion of antidepressants in the breast milk and their presence in the infant’s sera remains an ongoing concern, most women continue nursing while on medication. All antidepressant medications have “off-label” indications for their use in the perinatal population.

*Tricyclic antidepressants*

A relatively significant amount of data exists with regard to the safety of tricyclic antidepressants (TCAs) during pregnancy. Long-term studies of children exposed to TCAs in utero have shown no differences in intelligence quotient (IQ), language, temperament, or mood when compared with non-exposed children [66,67]. However, antenatal use of clomipramine raises concerns as it has been associated with congenital heart disease and transient adverse effects in neonates [68]. Nortriptyline has shown positive outcomes in the treatment of breast feeding mothers with post partum depression [69].

*Selective serotonin reuptake inhibitors*

The controversy surrounding selective serotonin reuptake inhibitor (SSRI) use in pregnancy continues to confuse both the treating clinicians and their patients alike. Recent US Food and Drug Administration (FDA) and Health Canada warnings regarding neonatal withdrawal in newborns exposed to SSRIs in the third trimester have caused alarm and discontinuation of pharmacotherapy [70,71]. Neonates with late third-trimester SSRI exposure have required prolonged hospitalization and respiratory support while experiencing symptoms such as apnea, irritability, and jitteriness. These effects were shown to be transient, with many babies who required acute obstetrical care returning...
home with their mothers in less than 48 h [72]. It is unclear as to whether these symptoms are a direct result of exposure or toxicity. Limitations of these case reports include a small sample size, incomplete information on important confounders, retrospective design, rating heterogeneity, reporting bias, and a lack of validation of fetal exposure [73]. It is worth noting that the severity of maternal illness itself has been associated with poor neonatal adaptation [74]. There are reports of a moderately increased risk of congenital malformations associated with prenatal exposure to SSRIs [75]. A small study showed that SSRI exposure might have subtle effects on motor development and motor control [76]. However, further studies are needed to confirm this risk and clarify whether it is attributable to the drugs themselves, underlying psychiatric disease, or to other factors. Finally, a study reporting an association between the maternal use of SSRIs in late pregnancy and persistent pulmonary hypertension, which led to the latest FDA/Health Canada warnings, has been found to have significant limitations including its retrospective design, recall bias, and small sample size [77].

On the one hand, there is literature showing a negative correlation between SSRI exposure during pregnancy and neonatal outcome, while on the other, ceasing pharmacological treatment in women with antenatal depression is associated with potential adverse effects for both mother and infant in the short- and long-term [78].

Recent reports in the New England Journal of Medicine suggest that the increased risks of malformations associated with SSRI use are likely small in terms of absolute risk [79].

Fluoxetine
More than 14,000 fluoxetine-exposed infants, who were evaluated prospectively, have shown no increase in the incidence of malformations [80–82]. However, minor congenital anomalies as well as neonatal toxicity or withdrawal symptoms have been reported in newborns subsequent to antenatal fluoxetine exposure [83].

With regard to the long-term effects of prenatal fluoxetine exposure, two separate studies compared a total of 95 fluoxetine-exposed mother–infant dyads, 16–86 months after delivery, with those exposed to TCAs and with a non-exposed control group. No differences in IQ, language, behavioral development, or cognition were noted between the three groups [66,67].

Fluoxetine use during lactation has been frequently studied. Although fluoxetine and its active metabolite norfluoxetine are excreted into the breast milk, few potential side effects have been reported [84]. Examination of the existing data shows some behavioral symptoms such as colic and hyperactivity [85], but the vast majority of studies show no adverse outcomes. As fluoxetine is the best-studied antidepressant during pregnancy with the most long-term follow-up data, clinicians often feel comfortable in prescribing it to this patient group.

Paroxetine
A US FDA/Health Canada warning based on the GlaxoSmithKline report has moved paroxetine to category D, indicating that the drug has been found harmful to human fetuses [86]. This report of 3581 pregnant women exposed to antidepressants in the first trimester showed an overall increased risk of congenital malformations, in particular ventricular septal defects (absolute risk 1.5% vs. 1%), with paroxetine use [86]. It is not clear whether a causal relationship exists. Fetal echocardiography is recommended for women who are exposed to paroxetine in the first trimester. In addition, several studies demonstrate the occurrence of neonatal withdrawal with paroxetine use in pregnancy [87,88], and one investigation showed an increased risk of neonatal withdrawal when this medication was taken in combination with clonazepam [72].

The data on paroxetine use in nursing women appear to be more favorable. Results of research on 77 paroxetine-exposed babies have shown almost undetectable medication levels in infants [89–93].

Sertraline
Current data on sertraline show that it is not associated with either congenital malformation or impaired neurological development in children [94]. Prior reports of withdrawal symptoms after prenatal exposure to sertraline have not been replicated by subsequent studies [95]. Sertraline levels in infants’ serum have been almost undetectable according to research on 146 babies [96–100]. As the placental transfer of sertraline is less than with other medications, and because of its safety profile in pregnant and breastfeeding women, it is the drug of choice for treating mood and anxiety disorders in this patient population.

The long-term neurobehavioral effects of prenatal exposure to the above SSRIs were examined in a study of 22 children, 14 of whom were exposed to paroxetine, five to fluoxetine, and three to sertraline [41]. No significant differences were found 4 years after birth between the exposed and non-exposed groups in terms of the children’s internalizing and externalizing behaviors; however, increased severity of maternal mood and anxiety disorders were associated with more problematic behaviors in these children [41,49].

Citalopram and escitalopram
A Swedish birth registry containing 375 women who had taken citalopram during pregnancy reported no apparent
risk to the newborn [88,101]; however, a case of infant withdrawal with prenatal citalopram use has recently been published [102]. Citalopram and its inactive metabolite desmethylcitalopram are excreted into human breast milk, and a case of sleep disturbance in an infant breastfed on citalopram has also been reported [103].

The safety data on citalopram are considered to be applicable to escitalopram, the S-enantiomer of citalopram. A woman who has responded to either of these medications should continue with the treatment during the perinatal period.

Serotonin norepinephrine reuptake inhibitors

Venlafaxine

Little is known about the potential short- and long-term effects of venlafaxine use in pregnancy. One study, examining 150 women exposed to venlafaxine during the first trimester of pregnancy, reported no increased incidence of birth defects [104]. However, two cases of neonatal seizures after in utero exposure to venlafaxine have recently been reported [105]. Neurodevelopmental outcomes appeared to be positive in these infants.

Ilett and colleagues have shown that concentrations of venlafaxine and its O-desmethyl metabolite were 2.5–2.7 times higher in breast milk than in maternal plasma [106]. However, drug exposure in breastfed infants was below the 10% notional level of concern. Low levels of the metabolite were detected in the plasma of four of the seven infants studied and, although no adverse effects were noted, breastfeeding infants exposed to venlafaxine should be closely monitored [106,107].

Mirtazapine

A recent prospective study of 104 women exposed to mirtazapine during pregnancy reported no apparent increase in the baseline rate of major malformations, although the study did report higher levels of spontaneous abortions in the in utero mirtazapine-exposed group than in a non-teratogen comparison group [108]. No published data are currently available on infant exposure to mirtazapine during the postpartum period.

Atypical antidepressants

Bupropion

Data from the manufacturer’s registry in June 2006 reporting on 621 first trimester exposures to bupropion noted incidents of cardiac defects, but these were not significantly higher than in comparison groups using other antidepressant medications [109]. A higher rate of spontaneous abortions was noted in 136 women exposed to bupropion during the first trimester of pregnancy; however, methodological limitations prevent definite conclusions [110].

To date, there have been no reported adverse effects regarding the use of bupropion during lactation [111]. If a woman is responsive to bupropion, switching to another medication is not recommended during pregnancy or lactation.

Trazodone

There has been no increase in birth defect rates in the 58 cases available involving trazodone use in pregnancy [112]. Long-term follow-up data are not yet available for this drug.

Conclusion

More than a century ago, Marcé made the connection between mental illness and the puerperium. Despite growing knowledge and understanding of the various disorders unique to this period in a woman’s life, effective treatment remains an enigma and the struggle to provide safe treatment to suffering women continues. This review endeavors to update clinicians on the current literature with a disclaimer that many questions remain unanswered. The choice of pharmacological treatment depends on the severity and chronicity of symptoms, the response to the medication, and its safety profile in the context of the current literature.

Disclosures

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Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials


Venlafaxine ER formulation is not supported for the treatment of major depressive disorder in children or adolescents, based on these two controlled trials.

Major depressive disorder (MDD) is common, even in youths. However, the available evidence for the use of antidepressants in children and adolescents is limited, and much past clinical practice has been based mostly on findings in adults. Recent warnings of the risk of suicidal behaviors in children and adolescents treated with antidepressant medications have led to a class-wide warning and controlled trials specific to these age groups are therefore urgently needed to determine the risk–benefit ratio.

Emslie and colleagues conducted two multicenter (50 sites), randomized, double-blind, placebo-controlled studies of venlafaxine-extended release formulation (venlafaxine-ER), given in flexible doses for 8 weeks (mean overall dose 97.1 mg; mean dose 80.4 mg and 109.2 mg for ages 7–11 years [children] and 12–17 years [adolescents], respectively). Subjects met DSM-IV criteria for MDD and had Childhood Depression Rating Scale–Revised (CDRS-R) scores >40. Psychotic disorders, bipolar disorders, and other DSM-IV Axis I disorders formed the exclusion criteria. The primary outcome measure was the change in CDRS-R score from baseline to week 8.

There was no statistically significant difference in the decrease in CDRS-R scores between those given venlafaxine-ER or placebo in either of the two age groups. However, in post hoc analysis, adolescents, but not children, treated with venlafaxine-ER had greater reductions in CDRS-R scores than placebo-treated patients. A greater number of serious adverse events were noted in the venlafaxine-ER-treated patients, including hostility, suicidal ideation, and suicide attempt. In addition, venlafaxine-ER-treated patients had higher rates of adverse events associated with study discontinuation.

Based on these trials, venlafaxine should not be considered a first-line treatment for MDD in children or adolescents. Even though there may be some potential efficacy in adolescents, as has been suggested in other reports, the consideration of side effects and serious adverse events makes the use of venlafaxine in these age groups less beneficial than in adults.

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Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study


This study demonstrates that venlafaxine use is associated with higher rates of suicide completion and attempts compared with other antidepressants. However, this is most likely because venlafaxine is prescribed to more severely ill patients with other risk factors for suicidal behaviors, rather than because of direct medication effects.

The recent concerns about antidepressant medications and increased risk of suicidal behavior in pediatric, adolescent, and young adult patients has prompted careful investigation of the factors that may be relevant in this association. All antidepressants, in addition to the selective serotonin reuptake inhibitors (SSRIs) with which this association first came to light, have now been tied to this warning, including antidepressants with varying mechanisms of action, such as bupropion, and medications with antidepressant effects but not considered antidepressants, such as quetiapine for bipolar depression.
Rubino and colleagues sought to investigate differences in the risk of suicide among antidepressant medications with varying mechanisms of action, including SSRIs (fluoxetine and citalopram), serotonin–norepinephrine reuptake inhibitors (venlafaxine), and tricyclic antidepressants (dothiepin).

Using data from the UK General Practice Research Database – an electronic medical record – prescriptions, clinical parameters, and attempted and completed suicides were collected for >200 000 patients aged 18–89 years, who had been prescribed one of the selected antidepressants between 1995 and 2005. Overall, 91% of the prescriptions were written for the treatment of depression. Fifty-four suicides and 3060 suicide attempts were identified. Suicide rates were found to be highest within 30 days of starting treatment.

Venlafaxine was associated with statistically higher rates of suicide completion and attempts compared with each of the other three medications. However, use of venlafaxine was also associated with higher rates of other severe risk factors in depression, including comorbidity with anxiety disorders, history of prior and multiple antidepressant therapy, history of psychiatric hospitalization, and family history of psychiatric illness. After adjusting for these risk factors, the suicide completion and attempt rates were still statistically significantly higher for venlafaxine compared with the other antidepressants, but the effect was greatly attenuated. Only selected risk factors were used in the hazard ratio correction, so it is possible that other non-medication factors may account for this misleading association with venlafaxine.

The authors of this study found that augmenting pharmacological treatments with intensive psychosocial therapy (cognitive–behavioral therapy, family-focused treatment, or interpersonal and social rhythm therapy) speeds and increases recovery in the treatment of bipolar depression.

Bipolar disorder accounts for approximately one-fifth of cases of depressive disorders. Few pharmacotherapy trials have focused on the treatment of acute bipolar depression, and even fewer psychosocial interventions have been studied in the acute phase of the illness. On the other hand, randomized, controlled trials have found that cognitive–behavioral therapy (CBT), family-focused treatment (FFT), interpersonal and social rhythm therapy (IPSRT), and group psychoeducation, combined with pharmacotherapy, are effective at preventing illness recurrence in this patient group. As part of the National Institutes of Mental Health-funded multicenter study, STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder), 293 acutely depressed patients with bipolar I or II disorder who were receiving treatment with standard mood stabilizers or other best-practice evidence-based pharmacotherapy were randomized to receive one of four psychosocial treatment interventions:

- Collaborative care (n=130).
- CBT (n=75).
- IPSRT (n=62).
- FFT (n=26).

Demographic variables did not differ between randomization groups. Collaborative care was the control condition, and consisted of three 50-min individual psychoeducation sessions that covered the major topics of the other therapies. Each of the targeted interventions (CBT, IPSRT, and FFT) consisted of up to 30 sessions of 50-min each with general psychoeducation followed by the more specific themes of each therapy: CBT focused on cognitive distortions and activity and skill deficits, IPSRT focused on disturbances in interpersonal relationships and social rhythms, and FFT focused on disturbances in family communication and relationships.

Overall, 67% of patients completed the full year of follow-up, with no differences in completion rates between treatment groups. Collaborative care patients completed a mean of 2.2 of the three sessions, whereas the specific therapy groups attended 14.3±11.4 of the 30 sessions. Patients also completed a mean 22.5±14.0 pharmacotherapy sessions during the year. By the end of the follow-up period, nearly 60% of patients had recovered from the depressive episode. Patients receiving CBT, IPSRT, or FFT recovered quicker and had higher recovery rates at the end of the study compared with those receiving the control condition. The study was not powered to detect differences between the intensive therapy groups.

This study suggests that intensive psychosocial interventions may improve outcomes in the treatment of acute bipolar depression. However, it was not clear whether the added benefit of the intensive therapies was related to any specific intervention, or just the additional number of psychosocial sessions compared with the control condition. A possibly important point is that other patients in STEP-BD did not appear to gain an added improvement associated with nonspecific psychotherapy. Nonetheless, data that positively affect therapeutic decisions for bipolar depression are fairly modest compared with those for major depressive disorders.
disorder, and this study clearly suggests that the addition of CBT, IPSRT, or FFT to pharmacotherapy when treating acute bipolar depression may improve outcomes.

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**Lithium treatment reduces suicide risk in recurrent major depressive disorder**


Lithium has been shown to have a significant antisuicidal effect in patients with bipolar disorder. The authors of this study therefore examined whether a similar effect could be achieved when lithium is used in the treatment of major depressive disorder (MDD). A MEDLINE search identified studies that examined the rate of suicide and attempted suicide in subjects with recurrent MDD, with or without lithium treatment. The Lucio Bini Mood Disorders Research Center (Sardinia, Italy) provided data on 78 additional subjects. Suicide rates were pooled and analyzed. A total of 329 subjects with MDD from eight studies were assessed. Subjects given lithium had an 88.5% lower rate of suicide or suicide attempt than those who did not receive this treatment. Completed suicide occurred at a rate of 0.17% and 1.48% per year, with and without lithium, respectively, translating into an 85% reduction in suicide rate attributable to lithium. Therefore, these results suggest that lithium may have an antisuicidal effect in recurrent MDD.

Although there is no substantial antisuicidal effect appreciated with the use of antidepressant medication in major depressive disorder (MDD), there is significant evidence that lithium has such a benefit in patients with bipolar disorder. The present authors conducted what they believe is the first meta-analysis on the possible antisuicidal benefits of lithium in patients with recurrent MDD. To this end, they searched MEDLINE from January 1966 to April 2006 for relevant articles. The rates of completed and attempted suicide were extracted from these studies, along with the levels of lithium exposure of the study subjects. Additionally, data from 78 patients with recurrent MDD who had been assessed at the Lucio Bini Mood Disorders Research Center (Sardinia, Italy) were included.

Results from eight trials involving 329 individuals were included in the final analysis. Of these subjects, 252 had received lithium treatment, 128 had been evaluated with and without lithium, and 205 had not been given lithium. In total, there were 6.27 years (1285 person–years) exposure without lithium and 4.56 years (1149 person–years) with lithium. Statistical analysis of the data revealed an 88.5% reduction in suicide attempts in those patients receiving lithium compared with those who were not treated with this drug. Additionally, among the six studies that assessed completed suicides, the pooled suicide rates were 0.33% per year for patients treated with lithium and 2.22% per year for those who were not. This is equivalent to an 85% reduction in suicide rate due to lithium.

This meta-analysis is the first of its kind to show a significant reduction in suicide attempts and completed suicides as a consequence of using lithium in the treatment of recurrent MDD. However, these findings are limited by the small number of pertinent published studies included in the final statistical analysis. Suicide rates may also have been under-reported in the pooled analysis as the majority of studies did not have suicidal behavior as a primary outcome measure.

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**Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial**


The authors examined the efficacy of atomoxetine in the treatment of binge-eating disorder in this randomized, double-blind, placebo-controlled study. Forty subjects were randomized to receive 10 weeks of either placebo (n=20) or a flexible schedule of atomoxetine (n=20). Subjects taking atomoxetine (mean dosage 106 mg/day) showed improvement in several measures of psychometric functioning and reduction in weight, body mass index, and binge day frequency. Four patients withdrew from the study due to adverse events. Of the three individuals receiving atomoxetine who discontinued the trial for this reason, each cited a different adverse effect: nervousness, constipation, and increased depressive symptoms. Therefore, the results suggest that atomoxetine is a useful and well-tolerated short-term treatment for binge-eating disorder.

The selective norepinephrine reuptake inhibitor atomoxetine has been associated with weight loss. These authors conducted a double-blind, parallel-group, randomized, outpatient, flexible-dosage study over the course of 10 weeks, in order to investigate this effect in patients with binge-eating disorder. The first phase was a screening period of 1–2 weeks duration, including a single-blind 1-week run-in of placebo to assess patients’ suitability for inclusion in the study.

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Evaluations included the Structured Clinical Interview for the DSM-IV to diagnose Axis I disorders, such as binge-eating disorder, physical assessments, including an electrocardiogram, blood and urine tests, and measurements of height and weight. Only subjects with at least three binge episodes and two binge days during the screening period were enrolled in the trial. Subsequent to assessments during this period, subjects were evaluated after 1, 2, 3, 4, 6, 8, and 10 weeks of treatment and 1 week after discontinuation of medication. Take-home diaries were given to patients to record binge episodes, and medication compliance was assessed by capsule count.

Of the 76 patients who were initially screened, 36 did not meet entry criteria or voluntarily withdrew. A total of 40 subjects were randomized to receive either atomoxetine or placebo (20 subjects in each group). Of these, 25 subjects completed the study – 14 in the atomoxetine group and 11 in the placebo group. Overall, the number of binges decreased in both groups, but more so in the atomoxetine group. The following variables were significantly improved in the atomoxetine group in comparison with the placebo subjects: body mass index (BMI), body weight, Clinical Global Impressions–Severity score, Three-Factor Eating Questionnaire hunger subscales scores, Yale–Brown Obsessive–Compulsive Scale-Binge Eating total and obsession subscale scores, and number of binge days per week.

In the atomoxetine group, 70% of the subjects had remission of binge episodes in the intent-to-treat population compared with 32% of subjects in the placebo group. A mean weight loss of 2.7 kg was noted in subjects in the atomoxetine group while no weight loss was observed in subjects receiving placebo.

Three subjects taking atomoxetine (compared with one in the placebo group) discontinued the study due to adverse events. These were different in each case, specifically nervousness, increased depressive symptoms, and constipation. There was no report of serious adverse reactions in any subject in the study.

This longitudinal, double-blinded study presents evidence that atomoxetine may have efficacy in the treatment of binge-eating disorder. However, the findings of the study are limited by the substantial dropout rate – 37.5% before completion of the study. Furthermore, binge-eating parameters were also assessed by self-report and may therefore be inaccurate. Since subjects with several common psychiatric disorders were excluded from the study, it is difficult to know how far these findings can be generalized.

Body mass index and risk of suicide among men
Mukamal KJ, Kawachi I, Miller M et al.

This is the third large epidemiological study that has found lower body mass index (BMI) to be associated with increased suicide risk in men, which differs from the positive relationship between BMI and suicide risk seen in women. Being overweight or obese carries significant medical risks, and may also have important associations with morbidity and mortality in psychiatric illnesses. Intuitively, it would be assumed that obesity is associated with greater risk of suicide than in the general population; however, previous studies have reported conflicting findings on the interaction between body mass index (BMI) and suicidality.

Mukamal and colleagues prospectively analyzed data from the HPFS (Health Professional Follow-up Study), which includes mailed questionnaire-based mortality and anthropomorphic data from a 16-year follow-up period for >50 000 male healthcare professionals, aged 40–75 years. BMI was self-reported. Deaths were confirmed by family report, postal officials, or the National Death Index. Suicide was classified by physicians unaware of the subject’s questionnaire results.

Out of >46 000 men without cancer and with completed questionnaires, the suicide rate was 19 per 100 000 person-years; 131 men completed suicide during the 16-year follow-up period. BMI was inversely related to the risk of suicide, so that for each one unit increase in BMI there was an 11% decrease in suicide risk. This finding remained significant, even when adjusting for medical illnesses, diet, antidepressant use, physical activity, and social support.

These results are similar to those of two other large studies, which found lower suicide risk associated with higher body weight. Magnusson and colleagues found that for every BMI increase of 5 kg/m², the risk of suicide decreased by 13% in 1 million men [1]. In a study of 40 000 individuals, Carpenter and colleagues also found an inverse relationship between BMI and suicidal ideation in men, but found the opposite relationship in women [2]. Thus, these three large studies have reported similar findings. One limitation of the current study is that suicide attempts and ideations were not measured. In addition, only a small proportion of the subjects were in the highest BMI group; therefore, different associations may still be present between BMI strata. Most interesting is the difference in this relationship between men
Salivary cortisol and psychopathology in children bereaved by the September 11, 2001 terror attacks

Pfeffer CR, Altemus M, Heo M et al.


Past research has shown that there is an increased risk of hypothalamic–pituitary–adrenal axis dysregulation, depression, and anxiety in children exposed to stressful events. These authors assessed 45 children who suffered the death of one parent as a consequence of the 9/11 terrorist attacks in 2001 and compared them with 34 children who were not bereaved. All children were assessed with standardized interviews and dexamethasone suppression tests, and salivary cortisol levels were assessed at 6-month intervals for 2 years. The results showed that bereaved children had increased rates of anxiety disorders, particularly post-traumatic stress disorder, after 9/11/01 compared with non-bereaved children. Cortisol levels were also higher in bereaved children.

Previously published research has suggested that the experience of bereavement prior to adolescence may predispose children to develop symptoms of mood disorders, particularly if the bereavement is due to a parent’s death. Additional research has also shown that stresses suffered in childhood may lead to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. The authors attempted to elucidate the relationships between psychiatric symptoms, HPA axis dysregulation, and parent death in children over the course of 2 years. Children from New York (NY, USA) who had lost a parent as a consequence of the terrorist attacks on 9/11/01 were assessed prospectively alongside a community sample of children who had not experienced the death of a close loved one.

A total of 45 children from 23 bereaved families and 34 children from 25 families who had not experienced bereavement were included. The families of the non-bereaved children all worked or lived close to the World Trade Center before or after 9/11/01.

All subjects were evaluated using various psychometric scales, including the Social Readjustment Rating Questionnaire for Children and the Child Schedule for Affective Disorders and Schizophrenia (K-SADS), every 6 months. Various physical parameters were also assessed, including body mass index and cortisol levels at baseline and after dexamethasone suppression.

Before 9/11/01, similar numbers of children in the non-bereaved and bereaved groups had a prior history of a psychiatric disorder – 35.3% and 31.8%, respectively. The most commonly reported psychiatric disorder was attention-deficit/hyperactivity disorder (17.7% and 13.6%, respectively). After the terrorist attacks, bereaved children were more likely to have a psychiatric diagnosis than non-bereaved children (72.7% vs. 35.3%, respectively). Anxiety disorders were more prevalent in bereaved children (56.8%) than in non-bereaved children (23.5%), particularly post-traumatic stress disorder (PTSD), which was present in 29.6% of bereaved children and 2.9% of non-bereaved subjects. Major depressive disorder (MDD) was found at higher rates in bereaved subjects but this was not statistically significant. The probability of having current MDD or current mood disorder was significantly higher in bereaved children compared with those in the non-bereaved group.

Throughout the study, baseline morning and afternoon salivary cortisol levels were higher in bereaved than non-bereaved children. This difference was not observed in evening baseline cortisol levels. Less suppression of salivary cortisol after dexamethasone was appreciated in bereaved children compared with non-bereaved children; however, this did not reach statistical significance. Dexamethasone suppression testing showed no significant difference between groups.

The relationship between the presence of psychiatric disorders and cortisol levels was assessed. A significant relationship was observed between generalized anxiety disorders and morning cortisol suppression. Subjects with PTSD without other psychiatric disorders had lower 4 PM cortisol levels and greater 4 PM cortisol suppression after dexamethasone suppression testing than those with other psychiatric disorders. The latter was also greater than the suppression observed in the combined groups of bereaved and nonbereaved children without other psychiatric disorders. Subjects with generalized anxiety disorders without comorbid psychiatric disorders had less suppression of morning cortisol after dexamethasone suppression testing than those children without any psychiatric disorders.

The small number of children diagnosed with several common psychiatric disorders, including MDD, limits these findings, making the relationship between cortisol levels and specific diagnoses difficult to determine.
Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States

Nemeroff CB, Kalali A, Keller MB et al.
Arch Gen Psychiatry 2007;64:466–72.

In this study, it was determined that the number of prescriptions for antidepressants to pediatric and adolescent patients with depression has decreased following the publicity surrounding the health advisories issued by the US Food and Drug Administration on the association of these medications with suicidality, compared with year-to-year increases in such prescriptions.

Since the US Food and Drug Administration (FDA) issued public health advisories in October 2003 and March 2004 concerning the occurrence of suicidality in pediatric and adolescent antidepressant clinical trials, there has been conflicting information as to whether prescribing trends have changed. Using data from IMS Health, Inc. (Norwalk, CT, USA), which is based on surveys of pharmacies, the US FDA asserted that prescriptions for antidepressants continued to increase by 7% yearly, and were not affected by the health advisories. However, two other studies performed in the same timeframe by Medco Health Solutions (pharmacy benefit claims) and NDC Health (prescription dispensing data), found decreases of 18% and 20%, respectively [1,2]. Nemeroff and colleagues sought to clarify this wide discrepancy by examining the Verispan (Yardley, PA, USA) database, which includes data from all US retail pharmacies and various payors (private insurance, Medicaid, or cash).

Verispan captures 1.4 billion prescriptions per year, which is approximately half of all US prescriptions. Data were analyzed from June 2000 (prior to the health advisories) to May 2005 (after the advisories) for three categorized age groups: <18, 18–25, and >25 years of age. From August to October 2003, the total number of antidepressant medication prescriptions began to decrease from the predicted previous trend line of prescription increases. The most dramatic effect occurred in patients aged <18 years, with a milder effect in those aged 18–25 years. Specifically, for patients aged <18 years, prescriptions decreased from monthly increases of 0.79% from April 2002–February 2004 to decreases of 4.23% after February 2004. Interestingly, the effect may have preceded the FDA health advisory announcements, but been related to the surrounding publicity. In addition, during the same period of time psychiatrists started providing a larger proportion of the overall clinical care for depressed patients, increasing from 44% to 63%.

Given the vastly superior completeness of the Verispan database compared with the original IMS Health dataset, it is clear that the publicity surrounding the two FDA health advisories has impacted upon psychiatric prescriptions and clinical care for pediatric and adolescent patients. However, the health warning considered only the potential risks of antidepressant medication usage, without careful balance with the potential benefits.


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Physical activity and common mental disorder: results from the Caerphilly study

Wiles NJ, Haase AM, Gallacher J et al.

The authors of this study explored the relationship between occupational physical activity, leisure time activity, and anxiety and depression. Data were collected from a cohort of middle-aged men from Caerphilly, UK. Subjects were followed for up to 10 years and screened for common mental disorders (CMDs; anxiety and depression) using the General Health Questionnaire. The Minnesota Leisure Time Physical Activity Questionnaire, a self-report tool, was used to estimate subjects’ total leisure time and percentage of leisure time spent doing heavy intensive activities. A total of 1158 men completed the study. Those initially reporting any heavy intensive leisure time activity had reduced odds of developing CMDs by 5 years follow-up. Upon analysis to compensate for missing data, this association weakened. Additionally, the data did not support the notion that men with the most physically demanding jobs were protected from CMD in the form of reduced odds of CMD development by 5 or 10 years. However, an association between heavy intensive leisure time activity and a small reduction in CMD after 5 years remained.

There has been some research on the association between mental health and physical activity; however, much of what has been published is fraught with experimental design limitations as well as conflicting results. The authors of this study examined the effect of physical activity on two common types of psychiatric disorders, depression and anxiety. They investigated a cohort of men for an association between reported time spent doing physical activities and the rate of these illnesses at 5 and 10 years.

Data were gathered from the Caerphilly Prospective Study, which included data on a cohort of middle-aged men in Caerphilly, UK. The study involved an initial survey, run
from 1979–1983, involving 2512 men living in this area aged 45–59 years (89% of those eligible). The second phase occurred 5 years after the initial data gathering, during which participants completed a questionnaire among other interventions, including blood tests and an electrocardiogram. The results served as baseline data for the longitudinal analyses run in the present study. Subjects were followed for two additional phases, 5 years apart.

The 30-item General Health Questionnaire (GHQ-30) was utilized in phases 2–4 to assess the incidence of CMDs, with a GHQ-30 score of ≥5 suggesting a CMD (specificity 71.0%, sensitivity 71.4%). Physical activity was measured in several ways. At baseline (phase 2), data on leisure-time physical activity were gathered using the Minnesota Leisure Time Physical Activity Questionnaire. Self-reporting modified from answers to the Health Insurance Plan questionnaire was used to measure physical activity at work, and included responses to questions on time was spent walking, sitting, and lifting at work. Occupational physical activity was divided into quartiles, with 1 being the least active. At baseline, 53% of subjects in the study were employed.

The data revealed that 68% of participants were involved in heavy intensive leisure-time physical activities and, overall, these men expended a median 254 kcal/day on leisure-time physical activity. Cross-sectional analysis resulted in several findings. There was a 34% reduction in the risk of CMDs in subjects in the highest third of total leisure time physical activity compared with the lowest third. There was an approximately 30% reduction in the odds of CMDs in subjects who reported any heavy intensive leisure-time physical activity.

At 5-year follow-up, longitudinal analysis revealed that subjects who did any heavy intensive leisure-time physical activity were less likely to develop CMDs, and this finding endured after restricting analyses to include only employed subjects. At 10-year follow-up, no association between CMD and leisure-time physical activity was seen; however, the data did show an approximately 70% increase in the odds of developing CMDs in subjects whose work involved greater levels of physical activity. This result was somewhat attenuated by correcting for confounding variables.

The findings of this study are limited by the assessment of physical activity being recorded at only one time point, and by the information on occupational physical activity coming from very basic questioning of subjects; recall bias is therefore possible. The results provide new data suggesting that heavy intensive leisure-time physical activity among middle-aged men is associated with a slight reduction in CMD at 5 years; however, this benefit was not apparent at 10 years.

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PROGNOSIS

Neural responses to happy facial expressions in major depression following antidepressant treatment


In this prospective study, the authors examined the relationship between brain regions identified as affected by antidepressant treatment and the processing of happy facial expressions. Nineteen medication-free individuals with depression and 19 healthy control subjects were examined using functional magnetic resonance imaging (fMRI) at baseline and 8 weeks into the study. Depressed subjects received 20 mg of fluoxetine daily from baseline. All subjects completed an fMRI task in which standard facial stimuli changed to display various degrees of happiness. The results revealed a restricted dynamic range of response in the extra-striate and limbic-subcortical visual regions of depressed patients compared with control subjects, which lessened after antidepressant treatment. These observed changes in neurophysiology suggest that, with treatment, there is a reversal of the impairment in processing of happy facial expression in depressed subjects.

According to previously published research, patients with depression have a reduced ability to distinguish facial affects. The present authors have previously reported data suggesting neural correlates for the ability to implicitly process sad facial expressions utilizing functional magnetic resonance imaging (fMRI) technology [1]. They had also previously discovered that treatment of depressed patients with fluoxetine resulted in attenuation of the altered activity in several brain regions. The authors present data on the same group of patients involved in the previous experiments, here examining their neural response to happy facial expressions.

Patients were screened for major depressive disorder using the Structured Clinical Interview for the DSM-IV and the Hamilton Rating Scale for Depression (HAM-D). All were free of psychotropic medications for at least 4 weeks at the time of recruitment. Nineteen subjects completed the entire study and 19 healthy, matched controls were also recruited. Subjects were examined with a structural MRI and three fMRI sessions, administered at baseline, week 2, and week 8, to examine the activation and dynamic range of brain systems thought to be involved in facial affect processing. Subjects in the depressed group received 20 mg fluoxetine daily and were assessed every 2 weeks using the HAM-D. A standardized set of happy facial expressions was morphed...
There have been several published studies suggesting that variations in the \textit{SLC6A4} gene locus are associated with differing responses to selective serotonin reuptake inhibitors (SSRIs) in the treatment of major depressive disorder (MDD). However, results from these studies have been inconclusive, in part due to small sample sizes and the fact that variation in this gene has not been systematically studied. The authors of the current study examined variants of the \textit{SLC6A4} gene in a large number of subjects with MDD who had well-characterized responses to the SSRI citalopram.

Outpatients (n=4041) were selected from the multicenter, prospective, randomized clinical trial, STAR*D (Sequenced Treatment Alternatives to Relieve Depression). DNA was collected from 1953 of these subjects. Tagging single nucleotide polymorphisms (SNPs) were used to assess the entire \textit{SLC6A4} locus, and DNA from the subjects was quantified utilizing polymerase chain reaction techniques. The authors used five definitions of citalopram response/phenotype. Responders were defined as those subjects who had a reduction of $\geq 50\%$ in their score on the Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR) on their last visit after 42 days of treatment. QIDS-SR scores correlate highly with scores on the more commonly used 17-item Hamilton Rating Scale for Depression. Subjects treated for $<42$ days were excluded from analysis. Remission was defined as a score $\leq 5$ on the QIDS-SR.

The results included data from 1914 subjects from whom DNA data was obtained. Of these, 1660 subjects could be categorized. There were 991 responders and 669 non-responders; 826 (83.3\%) of the responders were classed as being in remission.

The authors then postulated two additional definitions in order to attempt to separate true pharmacological responses from improvements due to placebo responses. “Specific” responders were defined as those subjects who had a response to medication that was maintained for all subsequent study visits following the first visit in which a response was recorded. “Non-specific” responders were defined as those who did not maintain improvement after an initial response was recorded. These categories were considered subsets of responders by the authors. Thus, of the 991 responders:

- 68.5\% (n=679) were specific responders.
- 18.9\% (n=187) were non-specific responders.
- 12.6\% (n=125) were unclassified.

Subsequently, the authors investigated an association between the patient response groups and \textit{SLC6A4} variants. The findings revealed no association between response and the 11 polymorphisms examined, even after accounting for confounding factors.
This study of a large sample of subjects treated for MDD did not show an association between any SNP within the SLC6A4 locus and response to citalopram. However, these findings are limited as there were several clinical and demographic factors by which the non-responders and responders differed, including schooling, length of current depressive episode, and baseline QIDS-SR score.

Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials


The authors of this report attempted a more balanced approach, considering both the benefit of symptom response and the risk of suicidality, in investigating antidepressant use in pediatric and adolescent patients with major depression or anxiety disorders. The data from this study indicate that antidepressants appear to have greater benefits (number-needed-to-treat 3–10) compared with risks (number-needed-to-harm 112–200).

In October 2003 and March 2004, the US Food and Drug Administration (FDA) issued two health advisories on the occurrence of suicidality in pediatric and adolescent antidepressant clinical trials. The FDA's actions were based on a one-sided analysis of the potential risks of antidepressant medications, leaving individual clinicians to balance these risks with potential benefits. However, without controlled trials specifically addressing the risks versus benefits of these medications, the overall trend has been of decreases in antidepressant medication use in pediatric and adolescent patients (Nemeroff et al. Arch Gen Psychiatry 2007;64:466–72; reviewed p127). Bridge and colleagues conducted an extensive meta-analysis of available data from 1998–2006, from published and unpublished randomized, placebo-controlled trials of second-generation antidepressants (selective serotonin reuptake inhibitors, nefazodone, venlafaxine, and mirtazapine) in patients who were aged ≤18 years with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or non-OCD anxiety disorders. The outcomes of efficacy and suicidality were compared across disorders. Fifteen MDD (n=3430), six OCD (n=718), and six non-OCD anxiety (n=1162) trials were identified as of generally good quality, and response data and rates of suicidality (suicidal ideation, suicide attempt, suicide preparatory behavior) were extracted.

The pooled response rate for MDD was 61% for antidepressants compared with 50% for placebo, and the number-needed-to-treat (NNT) for an additional responder was 10. The pooled response rate for OCD was 52% for antidepressants compared with 32% for placebo, and the NNT was six. Pooled response rates for non-OCD anxiety disorders were 69% for antidepressants and 39% for placebo, with a NNT of three. Thus, antidepressants had clinically significant benefit for all three types of disorder, with the greatest effect seen for non-OCD anxiety disorders.

Using the same data, the number needed to harm (NNH), i.e. for an additional adverse outcome of suicidality with antidepressants was calculated. The pooled NNH for MDD was 112, for OCD was 200, and for non-OCD anxiety disorders was 143. Compared with the NNT values, it was clear that the benefits of antidepressant use were greater than the risks. However, this direct comparison only considered the occurrence of medication response or suicidality. Clearly, completed suicide has an extremely high cost that needs to be accounted for in these comparisons. Put another way, even very rare occurrences need to be extremely carefully avoided if the consequences are grave. While this study provides some clarity to the discussion, further research is needed to address this controversy.

Clinical Reviews

Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression


The present authors found that brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with smaller hippocampal volume. However, the effect is not specific to patients with major depressive disorders, as control subjects carrying the BDNF-Met allele also had smaller hippocampal volumes.

PATHOGENESIS

Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression


The present authors found that brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with smaller hippocampal volume. However, the effect is not specific to patients with major depressive disorders, as control subjects carrying the BDNF-Met allele also had smaller hippocampal volumes.

Neurogenesis and neuroprotection are contemporary theories of the pathophysiology of major depressive disorder (MDD), based in part on evidence of hippocampal atrophy associated with MDD and neurogenesis associated with antidepressants. Brain-derived neurotrophic factor (BDNF) is purported to have a potential role in mood disorders, based on in vitro studies, animal models of depression, and the effect of some psycho-
tropic medications on BDNF. Frodl and colleagues sought to combine these lines of evidence, including hippocampal atrophy and the role of BDNFs in depression, to investigate the effect of the BDNF Val66Met polymorphism on hippocampal volumes in depressed patients and healthy control subjects.

Sixty patients with DSM-IV-defined MDD and 60 matched (age, gender, handedness, and alcohol use) controls were genotyped in order to identify them as either BDNF carriers or BDNF homozygotes. Hippocampal and amygdala volumes were compared between patients and controls, and between BDNF-Met carriers and BDNF-Val homozygotes.

Patients had mean illness duration of 6.7 years and mean Hamilton Depression Rating Scale score of 23.0. Allelic frequencies for both patients and controls were in Hardy–Weinberg equilibrium. The patient and control groups did not differ in the number of individuals who were BDNF-Met carriers. Patients had smaller hippocampal volumes than control subjects, but similar amygdala volumes. In both patient and control groups, BDNF-Met carriers had smaller hippocampal volumes; this effect was not different in patients compared with controls.

This study replicates prior findings of smaller hippocampal volumes associated with depression. However, it does not support the hypothesis that BDNF polymorphisms can explain the volume decreases specific to MDD. BDNF-Met carrier status may play a role in these smaller volumes, but in both patients and healthy subjects.

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Changes in depressive symptoms and glycemic control in diabetes mellitus

The authors of this study examined whether changes in depressive symptoms in patients with diabetes impact glycemic control. Ninety subjects with diabetes and a Beck Depression Inventory (BDI) score of >10 were assessed, and of these 65 completed 12 weeks of cognitive–behavioral therapy before reassessment of BDI scores. Depressive symptoms decreased significantly; however, fasting glucose and glycated hemoglobin levels did not change over time. Therefore, this study suggests that an improvement in depressive symptoms in patients with diabetes does not result in an improvement in glycemic control over the course of 1 year.

Previous research has offered confusing and even contradictory data on the interaction between glycemic control in patients with diabetes mellitus and the presence of depression. Some trials have found an association between certain measures of glycemic control (e.g. glycated hemoglobin [HbA1c]) and control of depressive symptoms, while others have not supported this theory. Additional studies suggest that the association is dependent on whether the patient has type 1 or 2 diabetes. In the current study, the authors investigated the effects of improvement of depressive symptoms with cognitive–behavioral therapy (CBT) on glycemic control in patients with diabetes.

Utilizing a single group, open-label design, subjects were assessed at baseline and after 12 months. Subjects were classified by the type of diabetes (type 1 or type 2) and were included in the study if they scored >10 on the 21-item Beck Depression Inventory (BDI). Among other variables, fasting blood glucose and HbA1c levels were assessed. Sixteen sessions of small group CBT were administered to patients. The BDI was repeated with each patient every 2 weeks until the end of the study. Average scores were calculated and compared with HbA1c levels drawn after 0, 3, 6, 9, and 12 months.

A total of 548 subjects were initially screened, and of these 415 were excluded based on the criteria of the study. An additional 43 subjects declined to continue, leaving 90 patients enrolled, 28 with type 1 and 62 with type 2 diabetes. The course of CBT was completed by 65 subjects and statistical analysis revealed no difference between outcome measures based on type of diabetes. BDI scores decreased from baseline, as did scores on the Hamilton Rating Scale for Depression (HAM-D), administered at baseline and after 3 months into the experiment. Conversely, there was no significant change in measures of glycemic control for patients with either type of diabetes. BDI score did not have a significant effect on HbA1c or fasting blood glucose level. There was also no association found between reductions in BDI or HAM-D scores and type of diabetes.

These findings suggest that treatment of depressive symptoms with CBT does not result in changes in glycemic control in patients with diabetes. There was also no apparent association between reduction in depressive symptoms and type of diabetes in this study. The results are limited by the small number of subjects with type 1 diabetes, reducing the statistical power of the trial to appreciate distinctions between the two forms of diabetes. Furthermore, there is a possible effect of self-selection as this study involved a substantial time commitment. Additionally, there was a significant reduction in subjects ultimately entered into the study due to the inclusion and exclusion criteria.

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Mania-like behavior induced by disruption of CLOCK
Roybal K, Theobold D, Graham A et al.

This study demonstrated that *CLOCK*-mutant mice exhibit the major behavioral manifestations of mania, including euphoria, decreased sleep, increased activity, increased risk-taking, and decreased anxiety, suggesting this to be the first robust animal model of bipolar mania.

A significant impediment to understanding the pathophysiology of bipolar disorder is the lack of a robust animal model; this also limits the development of new therapies. Major disruption of circadian rhythms, including sleep, appetite, and physical activity, characterize bipolar disorders. Thus, the *CLOCK* gene, which has been associated with mammalian circadian control, would be a reasonable target for investigation. Roybal and colleagues generated *CLOCK*-mutant mice in the hope of creating a clinically relevant animal model of bipolar disorder.

*CLOCK*-negative mice were created by *N*-ethyl-*N*-nitrosoourea mutagenesis. Homozygous *CLOCK*-negative male mice were compared with wild-type (homozygous *CLOCK*-positive) mice for behavioral profiles, reward behaviors, and mood stabilizer medication responses.

Overall, *CLOCK*-mutant mice showed a behavioral pattern suggestive of a robust model of mania. *CLOCK*-mutant mice had lower levels of anxiety than wild-type mice, as measured by open-field and elevated plus maze tests. Furthermore, when the mutant mice were given doses of lithium comparable with clinically therapeutic levels in humans (0.4 mmol/L), their anxiety levels normalized to near those of the wild-type mice. Other studies have found that much higher levels (1.3 mmol/L) of lithium suppresses activity in wild-type mice, whereas 0.8 mmol/L did not [1], suggesting that the levels of lithium given to these *CLOCK*-mutant mice did not simply sedate them. *CLOCK*-mutant mice also had lower levels of depression compared with wild-type mice, based on the Porsolt forced swim and learned helplessness tests, and were found to display a hyperhedonic state to a range of reward-testing stimuli (intracranial self-stimulation, cocaine, and sucrose tests). Other studies have reported that *CLOCK*-mutant mice require less sleep than wild-type mice. Infected these *CLOCK*-deficient mice with virally-mediated *CLOCK* gene transmission normalized their behavioral hyperactivity and anxiety levels.

Thus, the behavior of *CLOCK*-mutant mice was strongly suggestive of many aspects of mania, including decreased sleep, hyperactivity, decreased depression, increased pleasure seeking (possibly euphoria), and decreased anxiety. *CLOCK*-mutant mice may be the first robust animal model of mania, and if so, this would allow immediate probing of the pathophysiology of bipolar disorders. In addition, the availability of an animal model of mania will likely speed the development of novel treatments for bipolar disorders by providing a testing platform for new therapies.

**Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome**
Gothelf D, Feinstein C, Thompson T et al.

22q11.2 deletion syndrome has been characterized as a genetic risk factor for the development of schizophrenia. These authors examined 60 children, of whom 31 had the deletion and 29 had idiopathic developmental disability, using several psychometric measures to assess for early risk factors for the development of psychotic disorders. Fifty-one subjects were re-evaluated several years later. Scores on psychometric scales were similar at baseline; however, at follow-up 4.3% of subjects with idiopathic developmental disability had developed psychotic disorders compared with 32.1% of those with 22q11.2 deletion syndrome. In the 22q11.2 group, 61% of the variance in the severity of psychosis at the end of the study was predicted by an interaction between subthreshold psychotic symptoms, baseline depression anxiety symptoms, and the catechol-O-methyltransferase genotype. Increased severity of psychotic symptoms was also associated with lower baseline verbal IQ. These finding suggest that early intervention in children exhibiting subthreshold psychotic and internalization symptoms may be beneficial in reducing the risk of later development of psychotic disorders.

The syndrome known as DiGeorge syndrome, velocardiofacial syndrome, or 22q11.2 deletion syndrome is the most common human genetic disorder involving microdeletion, and occurs in 1 in 5000 births. It is associated with cognitive deficits and congenital malformations, and one in three patients develops psychotic disorders similar to schizophrenia. The present authors evaluated a cohort of subjects with the deletion syndrome for early signs of cognitive and thought disturbance, and compared them with children with idiopathic developmental disability. They also attempted to identify risk factors for the development of psychotic disorders in patients with 22q11.2 deletion syndrome.
During 1998 to 2000, 29 children with idiopathic developmental disability and 31 children with 22q11.2 deletion syndrome were recruited into the study. Twenty-three of those from the comparison group and 28 from the 22q11.2 deletion group were re-assessed in 2003–2005. The initial and follow-up assessments involved several well-established measures of cognition, development, and psychiatric well-being, including the Diagnostic Inventory for Children and Adolescents, the Child Behavior Checklist (CBCL), and the Wechsler Adult Intelligence Scale. Subjects in the 22q11.2 group were evaluated using magnetic resonance imaging scans.

The results showed no difference in the frequency of psychiatric illness between the groups at baseline; however, substantially more subjects in the 22q11.2 deletion syndrome group had developed psychotic illness by the end of the study, specifically schizophreniform disorder (n=2), psychotic depression (n=1), and schizophrenia or schizoaffective disorder (n=6). Psychotic depression was noted in one subject in the comparison group.

The only appreciable baseline difference between groups was higher CBCL externalizing scores in the comparison group compared with subjects in the 22q11.2 deletion syndrome group. There was group effect in the variables of externalizing, aggressive behavior, and total problem scales. These scores did not change in the 22q11.2 deletion group but did decline from baseline by the end of the study in the comparison group.

Regression analysis revealed that the catechol-O-methyltransferase (COMT) genotype, the presence of psychotic symptoms at baseline, and CBCL anxiety/depression subscale scores were associated with the diagnosis of a psychotic disorder at follow-up. Brief Psychiatric Rating Scale scores at follow-up were predicted by baseline CBCL anxiety/depression scores, COMT genotype, and psychotic symptoms. Of note, the relationship between baseline psychotic symptoms and psychotic disorders at follow-up was specific to subjects in the 22q11.2 deletion syndrome group.

These findings suggest that children with 22q11.2 deletion syndrome have more severe psychiatric symptoms than children with idiopathic developmental disability and are more likely to go on to develop psychotic disorders. Specifically, 32% of the children in the 22q11.2 deletion syndrome group developed psychotic disorders. Baseline psychotic symptoms interact with symptoms of anxiety and depression, as well as the COMT genotype, to substantially increase the risk of future development of psychotic disorders. This study stands as the first longitudinal analysis of the psychiatric symptoms of individuals with 21q11.2 deletion syndrome. However, the small sample size means that other possible risk factors for psychosis, such as variance in brain morphology, could not be taken into consideration.

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The 160th American Psychiatric Association (APA) annual meeting was held in San Diego (CA, USA). It provided a stimulating forum for presentation and debate of the latest international scientific advances in the field of psychiatry and related disorders, and gave insight into how this knowledge can best be used to continually improve patient care.

**STAR*D trial**
Forest Laboratories, Inc. (New York, NY, USA) supported a symposium that examined the findings of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial. STAR*D examined the efficacy of switching, combining, and augmenting therapies for depression in depressed patients who did not achieve symptom remission with their initial treatment. Grayson Norquist (University of Mississippi Medical Center, Jackson, MS, USA) began this interactive symposium by describing the study and welcoming audience members to participate in polling and questioning presenters.

Junius Gonzales (National Institute of Mental Health, Bethesda, MD, USA) examined the methods used to measure acute and long-term remission of depressive symptoms in the study, and then began an interactive discussion with audience members and other presenters on this topic. The STAR*D trial specifically employed several validated psychometric tools to examine any change in symptoms or side effects experienced by patients. The Quick Inventory of Depressive Symptomatology (QIDS) Self-Report and QIDS Clinician Rating were used to assess symptom severity. Side effects were assessed using the Frequency, Intensity, and Burden of Side Effects Rating scale. This instrument was also used to measure patient levels of functioning.

Marlene Freeman (University of Arizona, Tucson, AZ, USA) continued the discussion with an interactive examination of the selection of acute treatments between the first and second steps of the STAR*D trial. A John Rush (University of Texas Southwestern Medical Center, Dallas, TX, USA) further described the treatments used in the third and fourth steps of the trial, and K Ranga Krishnan (Duke University Medical Center, Durham, NC, USA) concluded the symposium by describing the decisions involved in assessing the risks and benefits of deciding whether to prescribe a patient with refractory depression a monoamine oxidase inhibitor, an atypical anti-psychotic medication, or to recommend electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), or repetitive transcranial magnetic stimulation (rTMS), in light of the findings of the trial.

**Treatment with neurostimulation**
A symposium focusing on treating refractory depression with neurostimulation technologies such as VNS, magnetic seizure therapy (MST), and rTMS was sponsored by Cyberonics, Inc., (Houston, TX, USA). Charles Nemeroff (Emory University School of Medicine, Atlanta, GA, USA) presented information on the mechanism of action of VNS therapy. This treatment was initially approved by the US Food and Drug Administration (FDA) in 1997 for the management of pharmacotherapy-resistant epilepsy, and is now indicated for treatment-resistant depression (TRD). It was initially found that patients being treated for epilepsy with VNS showed an improvement in depressive symptoms that was independent from the degree of seizure control obtained. Research has shown that VNS may result in effects on brain regions thought to be important in the pathogenesis of depression, namely the amygdala, the dorsal raphe nuclei, and the locus coeruleus. VNS also results in increased activity in neural circuits containing norepinephrine and serotonin.

Thomas Schlaepfer (University Hospital, Bonn, Germany) then discussed data on the efficacy of MST and rTMS. rTMS is an experimental technology that is being studied for the treatment of depression. It involves sending energy to areas of the brain thought to be involved in the pathophysiology of depression. Three small, blinded studies have shown an improvement in depressive symptoms with rTMS compared with placebo, as has a study comparing rTMS with ECT.
MST involves intentionally inducing a seizure after a muscle relaxant has been administered and while the patient is under anesthesia. Research examining the tolerability of MST suggests that attention and disorientation recovery, and retrograde and anterograde amnesia are significantly less after MST compared with ECT. A clinical trial for MST is currently underway.

Paul Holtzheimer (Emory University School of Medicine) presented research data on the efficacy of VNS in the management of TRD. In the context of this discussion, TRD was considered as depression that was inadequately managed by at least four antidepressant treatments. Open-label data from one trial showed a 50% improvement in Hamilton Rating Scale for Depression (HAM-D) scores for >30% of subjects receiving VNS for 10 weeks. A placebo-controlled study of VNS compared with usual care showed no significant improvement in depression after 10 weeks of acute treatment; however, those subjects who had open-label adjunctive VNS treatment showed a significant reduction in HAM-D24 score at 1-year follow-up. In another 1-year study, patients receiving VNS therapy and standard care had greater monthly improvement in depressive scores.

This symposium was concluded by Helen Mayberg (Emory University School of Medicine), who discussed the efficacy and mechanism of action of deep brain stimulation (DBS). This treatment has already received FDA approval in the US for Parkinson’s disease, and its efficacy in psychiatric disorders such as depression is currently being investigated. The subgenual cingulate (Cg25) area has many connections to areas of the brain thought to be involved in depression and the response to antidepressant treatment. Based on this, it was investigated as a possible locus for connectivity modulation by DBS in six patients with TRD. Four of the six patients experienced sustained remission of depression after chronic stimulation of white matter tracts adjacent to this brain region. Although this finding is encouraging, the invasive nature of DBS may limit its use in comparison with other neurostimulation techniques discussed in this symposium.

Geriatric psychiatry
Otema Adade (Duke University School of Medicine) presented research on social support variables as prognostic factors for the development of geriatric depression. Data on social support and depression were gathered on 1436 subjects aged >65 years who were living in the community, with follow-up assessments performed after 6 and 10 years. The data revealed that receiving instrumental assistance, perceived availability of supports, and perceived adequacy of support were predictors of depression at both follow-up points. Mental health services did not change the relationship between depression and social support. These findings suggest that lack of social support may be an important factor in the development of geriatric depression.

Pia Reyes (SUNY Downstate Medical Center, Brooklyn, NY, USA) presented research on the effect the interaction between depression and schizophrenia has on functioning in older adults. Symptoms related to depression (measured by the Center for Epidemiological Studies Depression scale), schizophrenia (measured by the Positive and Negative Syndrome Scale), dementia (measured by the Dementia Rating Scale [DRS]), and quality-of-life variables were examined in 55 subjects diagnosed with schizophrenia who were living in the community. These patients were compared with 113 matched control participants. Subjects in the schizophrenia group had lower scores in all DRS subscales, reported less confidants, and had lower instrumental activities of daily living scale scores compared with the control group. After compensating for negative symptoms, subjects in the schizophrenia group with positive symptoms had lower scores on the DRS as a whole and in the DRS conceptualization subscales, and also reported a lower number of confidants. This study suggests that individuals with schizophrenia have greater impairments in functioning than healthy controls, with patients with positive symptoms exhibiting the most impairment. Depressive symptoms in the absence of psychosis were not associated with increased functional impairment.

Sheryl Bedno (Walter Reed Army Medical Center, Silver Spring, MD, USA) presented research on the prevalence of depression in adults with or without diabetes mellitus (DM) from a military population. This case–control study compared adults aged >45 years who had type 2 DM with control subjects matched in terms of several variables of mental and physical health. The data revealed that 22.8% of subjects (n=13) with type 2 DM had been diagnosed with depression compared with 8.8% of control subjects (n=5). Subjects with DM accessed healthcare more often, and had increased hyperlipidemia, body mass index, and hypertension independently of the diagnosis of depression. Depressed subjects in both groups had increased primary care clinic visits. These findings show that the diagnosis of depression may increase healthcare utilization and that the diagnosis of diabetes may be more often associated with greater risk factors for cardiovascular disease.

Suicide
Jin-Jia Lin (Chi-Mei Medical Center, Tainan, Taiwan) presented data from a study examining the effect of limiting the availability of lethal methods on method-specific suicide rates. This study involved comparing the rate of suicide by hanging, a method believed to have equal access over time, with pesticide suicide rates after restriction of the availability
of pesticides. Age-adjusted rates of suicide by hanging or solid/liquid ingestion (mostly by pesticides) in Taiwan from 1983–2004 were investigated. There was a reduction in the graph slope of suicide rates by hanging and pesticides from 1983–1993. Specifically, the slope rates of suicide by hanging were –0.12 in women and –0.20 in men, while the slopes of rates of suicide by solid/liquid ingestion in women and men were –0.82 and –0.98, respectively. Regression coefficients for rates of suicide by solid/liquid ingestion compared with rates of suicide by hanging were –0.69 and –0.78 for women and men, respectively. These findings suggest that death rates for suicide by solid/liquid ingestion fell faster than those for suicide by hanging, implying that the restriction of pesticide availability may be an effective suicide prevention strategy.

Robert Kohn (Brown University, Providence, RI, USA) presented data from the Center for Disease Control on the epidemiology of suicide attempts and completed suicides in the elderly in the USA. Information was collected on emergency room surveillance data gathered from 2000–2003, and suicide fatal injury data was gathered from the Web-based Injury Statistics Query and Reporting System fatal database. A total of 1 446 031 suicide attempts were recorded, and these resulted in 123 072 completed suicides. Data were divided by age into the following categories: aged 25–59 years (adult), aged 60–74 years (“old”), and those aged >75 years (“old-old”). The suicide rate among women decreased with increasing age group but increased substantially among men from adult to old, and from old to old-old age groups. Self-harm decreased with increasing age in both men and women, while mortality from suicide attempts was substantially higher in the old and old-old categories. Men had considerably higher rates of suicide in all three groups compared with women. For example, the suicide rate among men in the adult group was 22.45 per 100 000 men, but 6.15 per 100 000 women. These findings suggest that the group with the highest suicide rate, the elderly, have fewer nonfatal attempts, resulting in higher mortality rates.

John Chelf (Laureate Psychiatric Clinic and Hospital, Tulsa, OK, USA) presented data on potential risk factors and the course of suicide ideation after inpatient psychiatric admission. Patients diagnosed with depression and admitted to an inpatient psychiatric unit for suicidal ideation (n=112) were assessed daily for 1 week after being discharged, and reassessed at regular intervals for up to 2 months. The Beck scale for Suicide Ideation (BSI) was utilized. BSI scores decreased from 20.2 on admission to 10.3 after admission then to 7.0 by 2 months later. Hospitalizations typically lasted 3–5 days, and by the second day of admission increased depressive symptoms, anxiety disorder, exposure to atypical antipsychotic medication during admission, and higher education levels were identified as independent predictors of less improvement in suicide ideation.

The following were identified as predictors of less improvement in suicide ideation after hospitalization: fewer visits to a psychiatrist, history of recurrent depression, and more prior admissions to a psychiatric facility. These findings suggest that suicide ideation shows greatest improvement within 2 days of hospitalization, and atypical antipsychotic medication use during hospitalization reduces the improvement in suicide ideation, even after adjusting for other variables.

Conclusion

There was a great deal of research on depression and related mood disorders at this year’s APA convention, including significant new data on the epidemiology of suicide and geriatric psychiatry. Observations on suicidality after psychiatric hospitalization are of particular note as they add empirical data to the utility of hospitalization in acute suicidality.

Data were presented on many aspects of depression, from genetic research on inheritance of mood disorders to research on the utility of short-term talk therapy in the treatment of depression. As the APA is an international forum for the presentation of new data and new ideas, no single theme would do justice to the myriad of research projects from around the world that were presented this year.
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