

DEPRESSION: Mind and Body

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

Editor-in-Chief

Alan F Schatzberg, Stanford, CA, USA

**Biological and Psychosocial Correlates of
Perimenopausal Depression: Implications
for Treatment**

LN Zappert and NL Rasgon

**Functional Neuroimaging in
Treatment-Resistant Depression**

JV Pardo et al.

**Psychiatric Disorders and the
Risk of Coronary Heart Disease**

A Nicholson

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Aims and Scope

Depression: Mind and Body is designed to bring a critical analysis of the world literature on depression, written by clinicians, for clinicians, to an international, multidisciplinary audience. Our mission is to promote better understanding of the treatment of depression across the global healthcare system by providing an active forum for the discussion of clinical and healthcare issues.

Leading Articles - These major review articles are chosen to reflect topical clinical and healthcare policy issues in depression. All contributions undergo a strict editorial review process.

Clinical Reviews - The most important papers 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 reportage from the most important international congresses.

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Dear Colleagues,

Welcome to the second issue of the third volume of *Depression: Mind and Body*.

The range of topics covered in this issue comprises mood disorders during perimenopausal depression, functional neuroimaging in treatment-resistant depression (TRD), and psychiatric disorders as risk factors for coronary heart disease (CHD).

In the first leading article, Laurel N Zappert and Natalie L Rasgon (Stanford University School of Medicine, Stanford, CA, USA) review the published data on biological and psychosocial correlates of mood disorders during perimenopause – the time when a woman undergoes the transition from regular menstrual cycles to the cessation of menstrual bleeding. The authors also discuss the treatment options in this area.

The second leading article, written by José V Pardo et al. (Minneapolis Veterans Affairs Medical Center and University of Minnesota, Minneapolis, MN, USA), provides a review of research into functional neuroimaging in TRD. Using a description of the structure and function of the neural systems relevant to depression as a basis for their review, the authors go on to assess two new electromagnetic treatments that show promise in TRD: repetitive transcranial stimulation and vagus nerve stimulation.

In the last of the three leading articles, Amanda Nicholson (University College London, London, UK) explores the relationship between CHD and depression, anxiety, and schizophrenia. As the author notes throughout the article, there are many aspects of this relationship that demand further research.

As always, the clinical reviews section provides concise coverage of the most important papers that have been published recently in the world literature on depressive disorders. Finally, Paul Ballas (Thomas Jefferson University Hospital, Philadelphia, PA, USA) describes highlights of the 65th Annual Scientific Conference of the American Psychosomatic Society, which took place in Budapest, Hungary, in March 2007.

We hope you enjoy this issue and welcome any comments or suggestions that you may have concerning the journal to help us continue to provide a useful and relevant review of current topics.

AF Schatzberg, MD
Editor-in-Chief

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REMEDICA 

Biological and Psychosocial Correlates of Perimenopausal Depression: Implications for Treatment

Laurel N Zappert^{1,2} and Natalie L Rasgon¹

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Perimenopause is the period of time when a woman undergoes the transition from regular menstrual cycles to the cessation of menstrual bleeding. During this stage of reproductive life, women can experience both somatic and psychological symptoms, such as hot flashes, breast tenderness, decreased libido, fatigue, worsening of premenstrual syndrome, irregular menstrual cycle, sleep problems, and mood swings. This article reviews data regarding the biological and psychosocial correlates of mood disorders during this period of transition in a woman's reproductive life and the implications for treatment. *Depression: Mind and Body* 2007;3(2):50–6.

Conflicting data exist regarding the increased frequency of psychiatric disorders during midlife in women [1]. However, those women who are psychiatrically vulnerable to hormonal changes may be at a higher risk for mood symptoms during the perimenopausal transition [1]. Perimenopausal mood symptoms may be related to female-specific mood disorders, such as premenstrual syndrome and postpartum depression, which occur during other periods of hormonal fluctuation in a woman's reproductive lifecycle [2–9]. In addition, certain psychosocial stressors can contribute to the development of mood disorders during this period in a woman's life.

Clarifying the associations between mood and hormonal status may improve the understanding of mood disorders during the perimenopausal transition. As life expectancy and the number of women entering midlife continues to increase, the identification, prevention, and treatment of perimenopausal-related mood disorders is becoming increasingly critical.

Biological factors related to midlife depression Major depression and women

The increased prevalence of major depression in women is one of the most consistent findings in affective disorders

research [10–13]. Beginning at puberty and continuing until menopause, women are twice as likely as men to suffer from unipolar major depression. Because this increased rate of depression is cross-cultural, researchers have long questioned the role of gonadal hormones in the differing rates of mood disorders. The theory that estrogen plays a role in mood regulation was first suggested at the end of the last century, when ovariectomized women were given extracts of animal ovarian tissue to alleviate psychological symptoms thought to be related to the removal of the ovaries [14]. While no consistent findings exist of a correlation between serum estrogen levels and severity of mood symptoms in non-surgical female populations, the theory that estrogen status affects mood in at least some women is supported by neurobiological studies in animals and humans and clinical data across the female lifespan.

Perimenopause and menopause

Numerous definitions of perimenopause exist in the medical literature, with studies citing it as a time period of as short as 2 years to as long as 15 years. For instance, Bastian et al. define the perimenopause as the year before the final menstrual period through the first year after the final menstrual period [15]. In contrast, the Stages of Reproductive Aging Workshop (STRAW) define it as the period of time from the first onset of menstrual irregularity to the year after the final menstrual period [16]. SWAN (the Study of Women's Health

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Across the Nation) breaks the menopausal transition into four categories: premenopausal (3 months of amenorrhea with no increase in menstrual irregularity in the past year), early perimenopausal (3 months of amenorrhea with some increase in menstrual irregularity), late perimenopausal (3–11 months of amenorrhea), and postmenopausal (≥ 12 consecutive months of amenorrhea with no medical cause other than menopause) [17]. In contrast, McKinlay et al. describe perimenopause as the stage of a woman's reproductive life that begins approximately 7 years prior to menopause, and is defined as the transition from regular menstrual cycles to the absence of menstrual bleeding [18].

As a result of these varying definitions, confusion regarding classification of menopausal status can lead to difficulties not only in diagnosing and treating midlife women, but also in conducting epidemiological and clinical research [17].

Common to all definitions is that during the perimenopausal transition the menstrual cycle becomes irregular as hormone levels fluctuate erratically due to intermittent ovulation [20]. The last 1–2 years of perimenopause are marked by a decreased output of estrogen, and it is at this stage that many women experience menopausal symptoms. During this time, women can experience both somatic and psychological complaints, including:

- Hot flashes.
- Breast tenderness.
- Decreased libido.
- Fatigue.
- Worsening of premenstrual syndrome.
- Irregular menstrual cycle.
- Sleep problems.
- Mood swings.

Postmenopause is defined by the absence of menstrual bleeding for 12 months and usually occurs between the ages of 45 and 55 years, with a mean age of 51.4 years [19]. During this time, degeneration of ovarian follicles occurs and estrogen levels decline [19,21].

Mood symptoms of perimenopausal transition

The influence of the menopause on rates of depressive disorders is more complex and multifaceted than previously thought. Menopause itself does not cause poorer psychological or physical health status [22], although during this reproductive stage some women do report mood symptoms, including depression, irritability, mood lability, and anxiety.

While studies vary widely in their methodology, definitions of menopausal status, and observed severity of depression among research subjects, the results of several

clinic-based surveys and epidemiological studies suggest that a significant number of women in the perimenopausal transition experience a clinically significant depression [7].

Furthermore, data suggest that certain risk factors predispose women to psychiatric complaints during menopause [21]. The risk factors for menopausal mood disorders include [1,19,23]:

- Personal or family history of mood disorder or mental illness.
- Ethnicity.
- Poor lifestyle habits.
- Psychosocial stressors.
- Impaired health.
- A history of mood symptoms during other times of hormonal change, e.g. during the late luteal phase of the menstrual cycle, pregnancy, and postpartum period.

The reported association between other reproductive endocrine-related mood disorders, such as premenopausal dysphoria and perimenopausal depression remains a source of controversy. This relationship is complex, evolving, and without definitive evidence that these conditions are necessary accompaniments of perimenopausal depression. For instance, a study of women with perimenopause-related depression found higher rates of premenstrual dysphoria and menstruation-related symptom cyclicality in depressed perimenopausal women compared with non-depressed perimenopausal women [24]. However, neither premenstrual dysphoria nor menses-related symptom cyclicality was always associated with perimenopausal depression. In contrast, Novaes et al. explored the relationship between a history of premenstrual symptoms and mood symptoms during perimenopause, and found that women who had experienced premenstrual dysphoria were more likely to present with psychiatric symptoms, especially depression, at menopause [6]. However, both of these studies were based on self-report, thus restricting the generalizability of the results.

Other factors have been shown to affect the incidence of depression during the perimenopause. In 1994, Avis et al. conducted a longitudinal follow-up analysis of data obtained from 2565 women aged 45–55 years in the Massachusetts Women's Health Study [25]. They found that women who experienced a long perimenopausal period (≥ 27 months) were at increased risk of depression. In addition, onset of natural menopause was not associated with increased risk of depression. Also a prior depressive episode was the variable that was most predictive of subsequent depression. In 2002, Dennerstein and colleagues reported that as women in their study progressed from the early stage of the menopausal transition to later stages, negative mood declined significantly,

while well-being improved significantly and positive mood did not change [26].

Overall, the contribution of menopause to depressive symptoms requires further examination. The investigation of risk factors to the development of perimenopausal depression may further guide the treatment of mood symptoms during this reproductive stage.

New onset of depression in the menopausal transition

In the past it has been unclear whether the perimenopausal period places a woman at increased risk for major depressive disorder (MDD), especially in those who have not had a previous episode of MDD. However, new evidence suggests that the menopausal transition may be associated with an increased risk of depressed mood in women who have never had a previous depressive episode [27].

In an 8-year longitudinal study, Freeman et al. investigated the associations of hormones and menopausal status with depressed mood in women without a previous history of depression [4]. Premenopausal women with no history of depression were enrolled and assessed using the Center for Epidemiological Studies of Depression (CES-D) scale to measure depressive symptoms and the Primary Care Evaluation of Mental Disorders (PRIME-MD) to identify clinical diagnoses of depressive disorders. High CES-D scores were ≥ 4 times more likely to occur during a woman's menopausal transition than during premenopause (odds ratio [OR] 4.29, 95% confidence interval [CI] 2.39–7.72; $p < 0.001$). In addition, a diagnosis of MDD was 2.5 times more likely to occur in the menopausal transition than in premenopause (OR 2.50, 95% CI 1.25–5.02; $p = 0.01$). These results suggest that the transition to menopause and its changing hormonal milieu are strongly associated with first onset of depressed mood in women.

In a longitudinal, prospective population-based study conducted at Harvard University (Boston, MA, USA), recently investigated the association between the menopausal transition and new onset of a first lifetime episode of MDD among women with no history of mood problems [27]. In this study, 460 premenopausal women between the ages of 36 and 45 years, with no lifetime diagnosis of MDD were assessed and followed using structured clinical interviews and the CES-D scale. After adjusting for age at the time of study enrollment and history of negative life events, the investigators found that women who entered the perimenopause were two-times as likely to develop significant depressive symptoms than those who remained premenopausal. Therefore, within a similarly-aged population of women with no lifetime history of depression, those who enter the menopausal transition earlier may have a significantly higher risk for first onset of MDD than those who enter the menopause at a later age.

Psychosocial factors related to depression

In addition to biological factors that may predispose women to mood disorders, environmental factors can also contribute to the development of a psychiatric disorder during the perimenopausal transition. These psychosocial stressors can have a significant impact on mood at a time when women may be more predisposed to psychiatric complaints due to changes in hormone levels. The association between demographic characteristics (e.g. socioeconomic status, marital satisfaction, ethnicity, quality of family relationships) and psychological and emotional well-being during the menopausal transition has been examined in several studies [28].

Some studies have suggested that during the midlife period, compared with other reproductive phases, women are more likely to experience negative life events such as a relationship loss (e.g. separation, divorce, loss of a parent, a child leaving home) or a role transition (e.g. returning to work after a child has left home, retiring) [29–32]. However, the differential effects of various stressful events on psychological well-being have not been consistently proven. For instance, Dennerstein et al. found that in women undergoing the menopausal transition, well-being was significantly affected by changes in marital status, life events, work satisfaction, and daily hassles [26]. In contrast, Schmidt et al. reported that while perimenopausal depression was associated with significantly more “undesirable life events,” it was not associated with loss events such as death, divorce, or “empty nest syndrome” (when children leave home) [32].

The validity of the “empty nest syndrome” theory should be addressed as it has been used for years to describe the psychosocial foundation of perimenopausal depressive symptoms [28]. Contrary to prior belief, women may not perceive a child leaving home as a stressful event [33,34]. Instead, a woman may perceive the perimenopausal period as a time of reduced psychological stress and an opportunity to increase social and leisure activities, improve romantic or marital relationships, or return to work [28]. Dennerstein et al. found that events such as a child leaving home were not always associated with negative mood [35], nor were they confined to this phase of a woman's reproductive life [32]. Further studies are needed to systematically evaluate whether the type or the frequency of life events modulates the risk of perimenopausal depression [32].

Treatment of depression in the midlife

Pharmacological treatments for perimenopausal depression include antidepressants, estrogen therapy (ET), or a combination of both. Research on the safety and efficacy of these treatments is on-going and some findings remain controversial. The following is a brief review of some but not all studies investigating the treatment of depression

during perimenopause with a focus on more recently published data.

Antidepressant use in the peri- and postmenopause

Antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), have been useful for the treatment of depression in perimenopausal or menopausal women [36]. While ET is an option for the treatment of mild depression in menopausal women, it alone may not be sufficient for more severe depression in this population. Currently, antidepressants are the recommended treatment for MDD in the menopausal transition, but the specific efficacy of certain antidepressants has not been examined in-depth in menopause-associated depression [37].

While there have been several studies examining the efficacy of antidepressants in the peri- and postmenopausal periods, to our knowledge no studies have compared the relative efficacy of different antidepressants in this population. In 2001, Joffe et al. examined the efficacy of mirtazapine in 22 perimenopausal and postmenopausal women aged of 40–61 years taking stable doses of ET, who met the criteria for MDD in an open-label clinical trial [37]. In all, 73% completed the 8-week trial, and remission of MDD was achieved by 14 of 16 (87.5%) women who completed the study. In addition, subjects responded well to mirtazapine regardless of whether their depression occurred before or after initiation of ET.

In 2003, Soares et al. investigated the efficacy of citalopram as monotherapy or as an adjunctive treatment to ET for perimenopausal and postmenopausal women with depression and vasomotor symptoms [38]. Thirty-five perimenopausal and postmenopausal women with MDD and menopause-related symptoms were administered 20–60 mg/day of citalopram alone (n=22) or as an adjunct to ET (estradiol [E(2)]) (n=13). Those who failed to show remission of depression after 4 weeks with ET alone were offered adjunctive treatment. Twelve women (92.3%) completed the 8-week adjunctive treatment, of whom 11 (91.6%) achieved full remission of depression.

After an initial 4-week treatment with ET monotherapy there was significant improvement in symptoms that had persisted (e.g. anxiousness, tension, tiredness, and difficulty in concentrating; $p < 0.05$). Thirteen of the 15 (86.6%) subjects who completed treatment with citalopram monotherapy showed full remission of depression. In addition, anxiety and other somatic complaints improved significantly ($p < 0.05$), while there was a trend toward improvement in vasomotor symptoms in those receiving monotherapy ($p = 0.06$).

Thus, citalopram alone may be an efficacious treatment for perimenopausal and postmenopausal-related depression. Furthermore, citalopram appears to be efficacious as an

adjunctive treatment for depressed subjects who remain symptomatic after treatment with E(2) alone.

Soares et al. more recently compared the efficacy of escitalopram to estrogen and progesterone therapy (EPT) for the treatment of peri- and postmenopausal-related symptoms (e.g. depression, sleep, vasomotor symptoms, and quality of life) in 40 peri- and postmenopausal women [39]. Subjects were randomized to an 8-week open trial of EPT (ethinyl E(2) 5 µg/day plus norethindrone acetate 1 mg/day) or escitalopram (flexible dose, 10–20 mg/day; fixed dose, 10 mg/day for the first 4 weeks). The authors reported that 75% (12/16) of subjects treated with escitalopram achieved full remission of depression compared with just 25% (4/16) treated with EPT. In addition, 56% (9/16) of subjects treated with escitalopram reported remission of menopause-related symptoms, compared with 31.2% (5/16) on EPT.

These results further add to the evidence that SSRIs are a viable treatment option for both depressive and vasomotor symptoms of menopause. More studies are needed to determine whether escitalopram is in fact superior to other SSRIs with regards to the treatment of both depression and vasomotor symptoms associated with the menopause.

Finally, the idea that perimenopausal mood disorders have a strong biological component that may be more resistant to the support and psychological components of the placebo response was supported by Burt et al. [40]. These authors examined the efficacy of duloxetine in the treatment of MDD in women aged 40–55 years compared with younger and older cohorts. The treatment response of 40–55 year olds taking 60 mg/day of duloxetine (n=55) and 62 placebo subjects were compared with that observed in women <40 years of age (94 placebo subjects and 85 duloxetine subjects) and women >55 years old (26 placebo subjects and 25 duloxetine subjects). Interestingly, compared with the placebo group, women aged 40–55 years receiving duloxetine demonstrated significantly greater improvement in total scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) at the 9-week study completion point.

Estrogen monotherapy for peri- and postmenopausal-related depression

As mentioned earlier, while ET alone may not be sufficient for more severe depression, it remains an option for the treatment of mild depression in menopausal women [37]. One of the earliest studies on the use of estrogen for treatment-resistant depression in premenopausal and postmenopausal women was performed by Klaiber et al. [41]. Although some women in this study clearly experienced significant improvement with estrogen treatment, the majority of ET-treated women remained highly symptomatic.

A series of trials have since been conducted with contradictory findings. Definitive analysis of these studies is hindered because of the use of different estrogen preparations, routes of administration, and dosages. Furthermore, these study populations have varied and included both perimenopausal and menopausal women, as well as women with varying intensities and frequencies of menopausal physical symptoms. Consequently, meta-analyses have been conducted in an attempt to evaluate these variables and the effects of estrogen on mood.

An earlier review of 111 studies on ET reported no consistent association between treatment and improvement of depression in women who had undergone natural menopause [42]. However, some effects were found for those women who had undergone surgical menopause [43]. A more recent meta-analysis of 26 studies suggested that ET is effective in reducing menopausal depressed mood [44]. The overall effect size for ET in this meta-analysis was 0.68, meaning that the average treatment patient had lower levels of depressed mood than 76% of the control patients. Analyses of the different hormone treatments revealed that estrogen alone had a larger effect size than progesterone alone or in combination with estrogen. Furthermore, the effect size was larger among perimenopausal women than among postmenopausal women.

While a review of all double-blind placebo-controlled studies published after the last meta-analyses is beyond the scope of this article, it is worth mentioning the findings of Soares et al. and Schmidt et al. [8,45]. These studies attempted to control for the problems of previous studies using homogenous perimenopausal populations and a transdermal route of administration of 17 β -estradiol.

In a double-blind parallel-design study, Schmidt et al. reported that 80% of subjects receiving E(2) had a full or partial therapeutic response compared with 22% of placebo subjects [45]. Nineteen out of 24 women with minor depression and six of seven women with a current diagnosis of MDD responded to active treatment. The effects on mood were independent of the presence of hot flashes or sleep disturbance, suggesting that ET may have an antidepressant effect independent of its effects on the physical manifestations of perimenopause.

Soares et al. investigated perimenopausal women with MDD (n=26), dysthymia (n=11), or minor depressive disorder (n=13) treated with 100 μ g of transdermal 17 β -estradiol. Remission was observed in 67% of the estradiol group compared with 20% of the placebo group (p<0.001) [8]. In this study, there was no difference in rate of improvement between those women with MDD vs. minor depression or dysthymia.

Finally, two open-label trials by Rasgon et al. and Cohen et al. investigated the effects of 17 β -estradiol on the course of depression in women in the menopausal transition [46,47].

Rasgon et al. treated 10 antidepressant and ET-naïve subjects with oral 17 β -estradiol (0.3 mg/day) alone and six women with treatment-resistant MDD with 17 β -estradiol as an adjunct to fluoxetine therapy [46]. All patients exhibited clinically significant improvement as measured by HAM-D scores after the first week of treatment. Of the 10 women receiving ET alone, six remitted, three partially responded to treatment, and one did not respond at the end of the 8-week treatment period. Of the six women receiving E(2) in addition to fluoxetine, one patient remitted and five had a partial response. This small study suggests that ET may have antidepressant efficacy for some antidepressant-naïve perimenopausal women with MDD.

The more recent study by Cohen et al. examined the effect of a 4-week course of transdermal 17 β -estradiol (100 μ g/day) on depression in 22 perimenopausal and postmenopausal women [47]. ET appeared to be most efficacious in the perimenopausal age group, since remission of depression was noted in six of the nine perimenopausal women compared with just two of 11 postmenopausal women. Therefore, depression in perimenopausal women may constitute a distinct reproductive cycle-related mood disturbance that may be responsive to ET.

Overall, further studies investigating the effects of ET in perimenopausal women are needed. The findings from the Women's Health Initiative (WHI) make it crucial to define the risks and benefits of ET to patients.

The initial findings from the WHI include the fact that hormone therapy (HT) is associated with an increased risk of heart attack, blood clots, stroke, breast cancer, and dementia in post-menopausal women. For those women taking part in the estrogen-only study, subjects had a higher risk of cardiovascular disease and more heart disease risk factors, such as high blood pressure, high blood cholesterol, obesity, and diabetes than those in the estrogen-with-progestin study. Current reanalysis of the WHI data has provided much needed clarification of these results. Indeed, an increase in the incidence of coronary heart disease is not the case in the cohort of women aged 50–59 years [52], but among women who started E/HT after the age of 60 years. These new results further highlight the importance of the timing of initiation of HT on health outcomes. However, risk of stroke was elevated regardless of the timing of HT initiation and/or type of therapy (e.g. estrogen-only or E/HT). Therefore, the position of the North American Menopause Society (NAMS) is that the WHI data should not be extrapolated directly to symptomatic perimenopausal women, women experiencing early menopause (aged 40–50 years), or to those undergoing premature menopause (<40 years old). Both the American College of Obstetricians and Gynecologists and NAMS recommend that E/HT should be used for the shortest

duration possible that is consistent both with treatment goals and risk–benefit assessments for individual women undergoing menopausal transition. More studies investigating different doses, drugs, specific preparations, administration methods, alternative therapies, and supplements are required as the specific algorithms for risk–benefit assessments of ET remain unclear.

Estrogen augmentation of antidepressants for MDD

It has been proposed that the decreased levels of estrogen associated with menopause may alter the response to serotonergic antidepressants [19]. The addition of estrogen is thought to have a role in augmenting SSRIs during the perimenopausal transition [19], and this hypothesis is supported by animal and human neurobiological and clinical studies [20].

In 2003, Grigoriadis et al. compared antidepressant response rates in women <44 (n=91) and >50 years of age (n=24) with a group of 86 age-matched men who met Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for MDD [48]. After 8 weeks of antidepressant treatment, younger women had significantly lower 21-item HAM-D scores and achieved significantly higher rates of remission compared with the older women. This pattern was not replicated in the male control group, which underscores the role of the estrogenic milieu in gender-specific antidepressant treatment response. This increased and more robust effect of antidepressants in the younger population, who thus have higher estrogen levels, further supports the hypothesis that estrogen may affect antidepressant response in women.

Another interesting finding is that the enhanced treatment response of antidepressants with estrogen may be specific to SSRIs. In 2000, Kornstein et al. conducted a large clinical trial of 235 men and 400 women with chronic major depression or “double depression” (major depressive episodes superimposed on dysthymia) [49]. The authors reported significant differences between pre- and postmenopausal women in the rate of response to sertraline. The investigators found that women were significantly more likely to show a positive response to sertraline than to imipramine, whereas men responded more favorably to imipramine. In addition, compared with postmenopausal women, premenopausal women responded significantly better to sertraline than to imipramine, while postmenopausal women had similar rates of response to the two medications.

The generalizability of these results, however, are limited. Although the researchers tried to control for the effect of exogenous hormone exposure (e.g. effects of oral contraceptives and ET) on response rates in premenopausal and postmenopausal women, the group sizes were too small to allow statistical analysis.

Finally, Rasgon et al. examined the efficacy of ET in the treatment of depression in 16 perimenopausal women who met DSM-IV criteria for MDD [46]. All patients exhibited clinical improvement as measured by HAM-D-21 scores after the first week of treatment. At the end of the trial, of the 10 perimenopausal depressed women receiving ET alone, six remitted, three partially responded to treatment, and one did not respond. Of the six women receiving antidepressant treatment with ET, one patient remitted and five had a partial response by the end of the trial. In depressed women who have minimal response to a SSRI, ET may augment response.

It should be noted that some data conflict with the augmentation data cited above. For instance, Amsterdam et al. retrospectively compared the efficacy of fluoxetine in women aged ≥ 45 years on ET (n=40) with ≥ 45 year old women not on ET (n=132), women <45 years (n=396), and in men (n=262) with MDD [50]. Efficacy rates were similar in all four groups. However, a major limitation of this study is that ET was given in a non-controlled fashion, as 63% of women received estrogen alone while 37% also took intermittent progesterone.

Overall, the evidence to support the efficacy of estrogen augmentation of antidepressants is not uniform. Thus, it would be premature to recommend estrogen as a primary treatment or as an augmenter of antidepressant response for all women.

Estrogen acceleration of antidepressant response for MDD

Just one study has examined estrogen acceleration of antidepressant response in women. While Kornstein et al. proposed an interaction between sex hormones and antidepressant response [49], a placebo-controlled study by Rasgon and colleagues showed that estrogen accelerated antidepressant response in 22 postmenopausal women with MDD [51]. Subjects received sertraline at 50 mg/day for 1 week with an increase to 100 mg/day at week 2 for a 10-week trial. Transdermal estrogen or placebo patches were randomly administered at the outset of sertraline treatment. Both groups showed a significant reduction in HAM-D-21 scores by study completion. However, women receiving sertraline in combination with ET improved significantly more rapidly than the women receiving sertraline with placebo. Therefore, ET may play a role in accelerating the antidepressant response in postmenopausal women with MDD. More placebo-controlled studies are needed to determine whether estrogen is a method for accelerating response to treatment.

Conclusion

In summary, the menopausal transition is associated with an increased vulnerability to a first lifetime onset or exacerbation of pre-existing depressive disorders. Numerous sociological,

psychological, and biological events may contribute to this increased psychiatric vulnerability, and the treatment of mood disorders in middle-aged women may also be influenced by these correlates. The use of antidepressants, specifically selective SSRIs, is a recommended treatment of depression in perimenopausal or menopausal women, but the specific efficacy of certain antidepressants has not been examined in depth in menopause-associated depression. ET used alone or as an adjunctive treatment to antidepressants is an option for the treatment of depression in menopausal women and warrants further investigation. Based on the recent findings from the WHI, it is crucial to define the risks and benefits of estrogen treatment and to identify the subset of subjects whose mood symptoms appear to be uniquely dependent upon estrogen status. Larger, more controlled, and longer longitudinal studies are needed to define women who are likely respond well to estrogen monotherapy and augmentation.

Disclosures

Dr Rasgon has served on advisory boards for Abbott Laboratories, Eli Lilly, GlaxoSmithKline, UCLA General Clinical Research Center Medical Advisory Committee, and Wyeth-Ayerst; consulted for Abbott and Wyeth-Ayerst; received funding or grants from Abbott, Forest, GlaxoSmithKline, National Institute of Aging, and National Institute of Mental Health; she has also participated in speakers bureaus for Abbott, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Pfizer, and Wyeth-Ayerst. Ms Zappert has no relevant financial relationships to disclose.

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Functional Neuroimaging in Treatment-Resistant Depression

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Functional neuroimaging has begun to make inroads into the clinical arena and to provide an important tool with which to study treatment-resistant depression (TRD). This progress has occurred despite inherent difficulties: lack of consensus about whether TRD is a specific disorder; variable definitions of TRD; presence of psychiatric comorbidities; lack of surrogate markers; paucity of genotyping; and the complex treatment and management issues presented by these often very ill patients. In this review, we first address the role of functional brain imaging in the management of TRD, which is not currently clinically indicated, using a case report that provides a model about how neuropsychiatric imaging is evolving toward clinical utility for other disorders. Subsequently, we review the neuroimaging studies of two new electromagnetic treatments that show promise in TRD: repetitive transcranial magnetic stimulation and vagus nerve stimulation. Neuroimaging has provided novel vistas of the relevant neural circuitry. Pregenual anterior cingulate hypoactivity tends to predict TRD. Successful treatment of TRD is associated with reduced ventromedial prefrontal metabolism that may be a final common pathway toward antidepressant effects and is associated with activity in the amygdala. This network is an important research focus and is currently being assessed in anatomical studies; functional, genomic, and molecular imaging studies; and neurophysiology studies. The nature of TRD demands such a multi-pronged approach to progress further in clinical care and scientific understanding of the illness. *Depression: Mind and Body* 2007;3(2):57–70.

Treatment-resistant depression (TRD), also known as treatment-refractory depression, is a common and serious clinical problem accounting for considerable morbidity and mortality in psychiatry [1]. Approximately 19–34% of patients treated with conventional antidepressants do not achieve remission [2]. One study showed that >80% of TRD patients treated as per the current standard of care (multiple medications; lithium or thyroid hormone boosts; electroconvulsive therapy) and followed for 2 years did not remit [3]. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial reported remission rates of 37%, 31%, 14%, and 13%, respectively, after each of the four successive treatment steps [4]. This suggests that patients who do not respond to the first two interventions are less likely to respond to further treatments.

Although several staging systems have been proposed for TRD [5–7], the precise definition usually needs explicit delineation. The antidepressant trial must have been adequate in dose and time, and not terminated prematurely because of intolerance to side effects. What often appears as TRD is misdiagnosis or undertreatment [8].

Misdiagnosis and undertreatment of TRD

The clinician must always revisit the issue of an incorrect diagnosis leading to suboptimal therapy. In one series, one-third of patients referred to a specialty mood clinic with some level of treatment resistance, and who were deemed to have “definite” or “highly probable” bipolar disorder by the consultant, had never been treated with a mood stabilizer [9]. There was also a high prevalence of secondary psychiatric conditions that were thought to have a significant role in the primary diagnosis of depression. These included generalized anxiety, panic, obsessive-compulsive, eating, and personality disorders, and social phobia. Another study

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documented the high comorbidity between substance abuse and anxiety disorders in TRD [1]. The comorbidity with personality disorder can predict a poorer treatment response, slower therapeutic change, poorer compliance, and greater functional impairment [10]. TRD patients frequently appear to have a primary personality disorder so a careful developmental history, particularly for the teenage years, becomes essential to prevent misdiagnosis. Here, family members can provide a key perspective on global assessment of function during development into young adulthood.

Failed trials resulting from non-compliance are another source of undertreatment. Unfortunately, serum blood levels of antidepressants are probably underused in guaranteeing compliance. Low blood levels despite adequate drug dose can occur from ultra-rapid metabolism from hepatic enzyme induction (e.g. smoking) or P450 genotype [11]. In fact, genotyping of P450 enzymes has only recently become widely available and provides another tool with which to tailor dosing. Genotyping of other alleles, such as the polymorphisms of the promoter for the serotonin transporter (5HTTLPR), to guide optimal drug therapeutics is in its infancy.

Functional neuroimaging of TRD

This review will focus on the role of functional imaging in TRD. Given the clinical importance of this illness, there is an alarming paucity of such studies caused by several issues besides the inadequate funding of research. The frequency with which comorbidities occur in patients with TRD prevents the clean dissection of the data. Additionally, in order to look for changes in brain function associated with treatment, a washout period is typically necessary. Although some TRD patients will gladly discontinue medications that are not working, patients withdraw from studies at a high rate during washout of medications; few can go completely without anxiolytics or hypnotics. With dropout rates of up to 50%, the ability to generalize the results to the general population becomes limited. The patient typically needs to be seen at least weekly at the start of such a study, with frequent assessment of suicide risk. Some argue that there is inadequate evidence to study TRD as a discrete syndrome [12]. Furthermore, the last several years have highlighted that selecting homogeneous groups based upon genotyping of key candidate genes (e.g. 5HTTLPR) will become necessary to properly define the subjects enrolled. Of course, this is difficult to do when many key genes remain unknown.

What is the purpose of neuroimaging TRD? Broadly speaking, the need is two-fold: clinical and scientific. Clinically, neuroimaging might enable early detection and prevention; improved diagnosis; treatment selection that is not based upon trial and error; prognostication; and the development of novel therapeutic strategies. There is a paucity of surrogate markers

in psychiatry. A neuroimaging surrogate marker should have biological plausibility, predict disease progression and outcome, and be easily measured with standard imaging protocols.

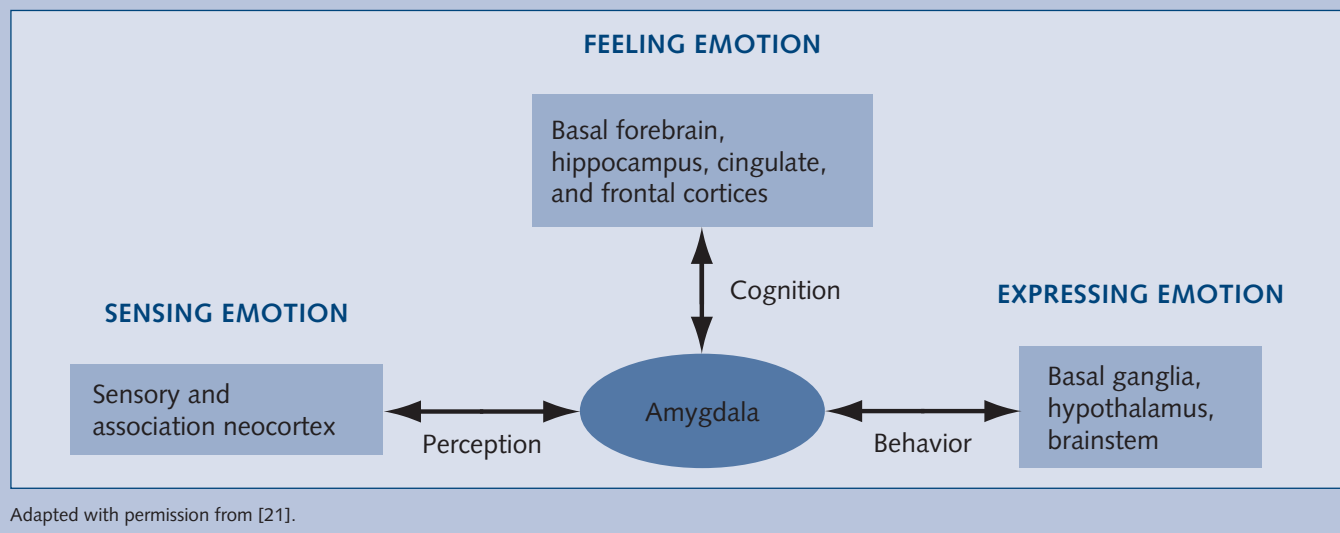
Regional cerebral glucose metabolism (rCMRglu) in the pregenual anterior cingulate has been proposed as a predictor of treatment response [13,14]. However, the large overlap in variance between patient and control groups prevents using this marker for diagnosis in individual cases. Similarly, sustained low activity in the subgenual cingulate with high activity in the amygdala while processing negative stimuli has been shown to be predictive of response to cognitive behavioral therapy (CBT) [15]. Another example arises in the development of novel experimental treatments, such as deep brain stimulation (DBS) of white matter tracts in the pregenual or subgenual cingulate cortices, guided by prior neuroimaging research [16,17].

Neural structures relevant to TRD

It is impossible to review functional neuroimaging studies of TRD without mentioning anatomical structures that were essentially uncharted 15 years ago. A wealth of information about both the structure and function of the neural systems relevant to depression has arisen in the past decade. Broadly, the prefrontal cortex (PFC) can be divided into dorsal regions that support "higher" cognitive functions (such as working memory, attention, and language) and ventral regions that appear to be involved in affect, decision-making, social behavior, sensitivity to environmental influences (e.g. stress, approach, and avoidance), and personality. Much less is known about the ventral than the dorsal regions, despite the former bearing most relevance to psychiatric disorders. On a basic level, depression is associated with hypoactivity of the dorsal regions, producing cognitive dysfunction, and with hyperactivity of the ventral prefrontal regions, whose functional sequelae remain largely unknown [18]. Antidepressants appear to correct this imbalance by diminishing ventral and increasing dorsal neural activity (reviewed in [18]).

Two major components of the ventral system include the ventromedial PFC (VMPFC) and the amygdala, which are densely interconnected both anatomically and functionally and are highly relevant to affective illness. For example, genetic polymorphisms associated with sensitivity to stress and depression (e.g. 5HTTLPR) robustly modulate the functional connectivity between the two regions (e.g. [19]). Research has shown that women, but not men, have high functional connectivity between these two structures in the resting brain, perhaps indicative of the greatly increased risk of major depressive disorder (MDD) in women [20]. As will be reviewed, neuroimaging studies of patients with affective illness frequently point to the amygdala and VMPFC as critical members of a circuit that participates in the regulation of affect.

Figure 1. A simplified cartoon of the tripartite organization of neural systems in affective processing. The amygdala plays a central role.



Amygdala

Scientifically, functional neuroimaging has defined some of the relevant circuitry of affect. The amygdala, an almond-shaped structure in the medial temporal lobe that contains >12 subnuclei in itself, is a key player in affective processing. Each amygdala measures 15 mm in length and 10 mm in width at its maximum and has a volume of approximately 1.1 mL. At the current level of resolution in brain imaging, only neural activity in the structure as a whole can be mapped.

The amygdala plays a central role in affective processing, including emotional expression, perception, and feeling (Fig. 1) [21]. The circuitry for emotional expression includes the basal ganglia, hypothalamus, and brainstem. Since motor behavior is readily quantifiable and does not require introspection, these studies come largely from animals. Among the most studied paradigms of amygdalar integration of observable behavior are conditioned fear [22,23], learned helplessness [24,25], and maternal separation. Studies in primates have shown that disruption of the maternal–infant bond increases depressive and anxiety behaviors [26,27]. Although the dissection of this process at the molecular level has just begun, this early disruption appears to modulate amygdalar transcription with decreased expression of guanylate cyclase 1 α 3 in the lateral and basal subnuclei of the amygdala [28].

In contrast with the animal work, cognitive activation studies in healthy human volunteers have enabled the identification of many structures used to sense or perceive emotion, including the uni- and polymodal sensory cortices and the amygdala [29–42]. For example, we have shown that aversive olfactory and auditory stimuli robustly (i.e. a >10% change in regional cerebral blood flow [rCBF]) activate the human amygdala and associated sensory

cortices [43,44]. The rCBF change in the amygdala during olfaction correlates with perceived aversiveness. With some exceptions (e.g. [30,45–49]), the study of the experience or feeling of emotion has focused on patients with mood and anxiety disorders. One prominent approach has been symptom provocation [32,50–52]. The patient can tell the investigator about their mood using a variety of scales. Additionally, the signs and symptoms can be observed directly during the symptom provocation.

Ventromedial prefrontal cortex

Densely connected to the amygdala is the VMPFC [53]. Based upon cortico–cortico connectivity, cytoarchitecture (frequently termed Brodmann areas [BAs]), myeloarchitecture, and chemoarchitecture, Price et al. have provided evidence for considerable evolutionary homology of the VMPFC, particularly with respect to the human and non-human primate [54,55]. The ventral prefrontal cortex contains two networks: the VMPFC and the orbitoprefrontal cortex (OPFC; Fig. 2). Each of these networks has dense intrinsic connectivity and interacts with the other to some degree. The VMPFC largely encompasses BA 24a, 10m, 10r, 10o, 32m, 14r, 14c, 13a, 13b, 11m, 1ai, 47/12s, and 25 (the subgenual cingulate). The VMPFC also interconnects with the periaqueductal gray (PAG) and hypothalamus, which in turn interconnect with the amygdala. The VMPFC contains a couple of parallel subnetworks based upon connections to distinct columns within the PAG [56]. Unlike the OPFC that connects to sensory association cortices, the VMPFC receives no direct sensory projections. In contrast, the VMPFC receives sensory information only after processing in the amygdala or from polysensory anterior temporal regions. The VMPFC is well poised to relate the internal milieu to sensory-related

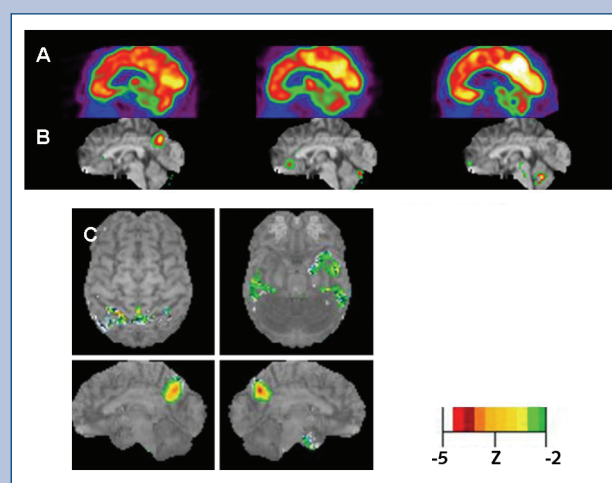
Currently, abnormalities in glucose metabolism are detected by visual inspection of the PET scan alone. Research is underway to develop quantitative methods in place of visual inspection in the hope that they may provide greater sensitivity and specificity. For example, as part of the National Institutes of Health Human Brain Project, normative databases of brain glucose metabolism have been built using PET (see <http://james.psych.umn.edu>, [75]). The subjects were examined and screened medically (physical examination and laboratory studies), neuropsychologically, and psychiatrically (structured diagnostic interviews). All brain scans were warped using computer methods to a standard stereotactic template, so that each subject's anatomy was precisely normalized and aligned [76]. Of note, this method requires that the patient's gross brain anatomy approaches normal morphology. In the case of early dementia and other neuropsychiatric disorders, this requirement appears reasonable, but the benefits of imaging for early diagnosis and treatment become moot in the case of an "end-stage" brain.

Each volume element (voxel) in the image contains the mean and standard deviation of glucose metabolism from the normative database. A patient's PET scan is warped to the same template. Z-scores (the difference between the patient's metabolism and the reference group's mean metabolism divided by the reference group's standard deviation; in other words, the number of standard deviations the patient's metabolism deviates from the reference group) are calculated after regressing on (adjusting for) age [77].

Figure 3 depicts an example of a difference scan. The threshold determines the minimum level of metabolism displayed over the template MRI. In other words, any activity below the threshold is not shown overlaid on the MRI template or the patient's own MRI. The precise threshold value can be adjusted depending on the desired sensitivity and specificity. For display purposes, here we used a threshold of $Z=2$. The patient, a 73 year old, retired, chemical engineer presented with subjective memory complaints with no deficits in his activities of daily living. He scored 28/30 in the Mini Mental Exam [78] and did not even meet criteria for mild cognitive impairment (MCI) [79]. Although no changes were visible in the unprocessed image, the results after processing were clearly consistent with either Alzheimer's disease or early Lewy body dementia, not frontotemporal dementia. The patient showed characteristic metabolic changes in the medial and lateral posterior parietal cortices [80–82]. He converted from his "pre-MCI" status to MCI approximately 1 year later, and within 6 months met criteria for Lewy body dementia with fluctuating cognition, visual hallucinations, Parkinsonism, and rapid eye movement sleep behavior disorder.

This case illustrates what is possible in clinical neuroimaging of psychiatric disorders, specifically the

Figure 3. Detection of earliest brain changes in a dementing illness as a prototype toward clinical neuropsychiatric imaging [75]. A 73 year old man with mild memory complaints who did not even meet criteria for mild cognitive impairment underwent fluorodeoxyglucose (FDG) positron-emission tomography. **A:** Sagittal section of patient's raw FDG image (left) after stereotactic and whole-brain normalization next to images (center and right) from two other matched controls. Visual inspection of the images alone does not highlight the patient's abnormality. **B:** Difference image of each person in A compared with normative database (35 healthy subjects with age regression) showing hypometabolism in medial posterior parietal cortex – a pattern frequently seen in early Alzheimer's disease or Lewy body dementia. **C:** Surface projection of patient's hypometabolic regions with color scale ($-5.0 \leq Z \leq -2.0$).



potential for early detection when therapeutics might still have a chance to work. The detection of Alzheimer's disease and Lewy body dementia using PET remains investigational at this time. There is no clinical indication to use any functional imaging procedure in the assessment of any psychiatric disorder other than in the specific case of differentiating Alzheimer's disease from frontotemporal dementia when traditional tests leave the diagnosis uncertain. Although there is much cause for optimism, we are years away from application to other psychiatric disorders.

Functional imaging of TRD: a selective review

Functional imaging studies require some knowledge about the underlying structural changes associated with TRD (e.g. atrophy). Some relatively early publications, although not specifically about TRD, suggest that a variety of structural changes seen in the elderly predict a more treatment-resistant prognosis. These changes, seen with either computed tomography or MRI, include ventricular enlargement, cortical atrophy, subcortical white matter lesions (particularly

in the basal ganglia), and white matter hyperintensities. This literature, which focuses more on geriatric depression, is beyond the scope of this report (for a review see [83]). Likewise, abnormalities seen with neuroimaging in depression without specific relationship to TRD (e.g. changes in amygdala or hippocampal volume) will not be reviewed.

A mediating role for “vascular depression” in the perpetuation of depression has been hypothesized [84]. However, opinions on this matter are divergent. For example, data from one study found no evidence that white matter hyperintensities or minor ischemic lesions played a role in late-onset depression [85]. Another study showed that retinal microvascular abnormalities, which reflect the condition of the cerebral vasculature, did not associate with depression symptoms in the elderly [86].

There have been several studies of brain structure specific to TRD. For example, Shah et al. studied 20 patients, aged 21–65 years, with depression lasting ≥ 2 consecutive years meeting Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria [87]. Treatment-resistance was defined as failure of at least two adequate trials of four possible regimens that included tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAOIs); selective serotonin reuptake inhibitors (SSRIs); and electroconvulsive therapy (ECT). All chronically depressed subjects were on medication. In addition, these patients were matched with 20 healthy controls and 20 patients in remission from depression (some medicated, some not). All subjects underwent assessment with a neuropsychological battery. Analysis was carried out using voxel-based morphometry (VBM) of the gray matter and the images corrected for slight imperfections in the magnetic field of the MRI machine. The scans were classified (segmented) into gray and white matter, as well as cerebrospinal fluid (CSF). The most robust finding in the TRD group was a reduction in gray matter density in the left superior temporal gyrus. Additionally, a significant correlation was found between performance in a delayed verbal recall task and gray matter density in the left hippocampus ($p < 0.04$).

In a re-analysis of these data, Shah et al. demonstrated right frontostriatal atrophy in the same patients when using “gold standard” volumetry (hand tracing) and additional measurements of CSF and white matter [88]. It was hypothesized that the previously reported left temporal reductions from VBM analyses did not appear in the traditional volumetric analysis because there was no corresponding increase in CSF. A more complex statistical parametric mapping analysis using SPM96 (Wellcome Department of Cognitive Neurology, London, UK), including all three tissue compartments (gray matter, white matter, and CSF), showed a reduction in left hippocampal gray

matter with reciprocal white matter increase (suggestive of a change in tissue composition); left superior temporal and pre-central gray matter reduction; right superior and medial frontal white matter reduction; right superior frontal gray matter reduction with reciprocal CSF increase (suggestive of atrophy); and left frontal CSF increase with a left medial (BA 24) and superior frontal white matter increase (suggestive of change in tissue composition).

There are numerous studies of both resting and cognitive activation paradigms dealing with affective processing and unipolar patients. Although these are beyond the scope of this review, the relevant literature indicates that the proper interpretation of imaging results requires careful attention to the diagnosis under study, in addition to comorbidities, symptom severity, medication status, chronicity, and treatment resistance.

In one of the first studies looking at the brain correlates of TRD, Hornig et al. used hexamethylpropanolamine (HMPAO) single-photon emission computed tomography (SPECT), a measure of rCBF [89]. The unmedicated control group consisted of nine men and seven women, aged 24–62 years, none of whom had a history of Axis I (other than depression) or Axis II disorders based upon semi-structured interviews, and who were demographically similar to the treated patients. The patient group comprised 14 men and seven women aged 24–59 years who, without medication for 2–4 weeks, met DSM-IV criteria for MDD with a 17-item Hamilton Depression Scale (HAM-D₁₇) score ≥ 17 . The patient group was further subdivided into TRD ($n=8$) and non-TRD ($n=13$) groups, as defined by a history of one failed prospective trial of at least 6 weeks duration using adequate doses either in the current episode or the previous episode. In the TRD group, the mean duration of the current episode was 61 weeks (range 8–260 weeks), compared with 64 weeks (range 6–156 weeks). Patients in the TRD group had failed an average of 10 previous antidepressant trials (range 3–19). The number of failed trials for the non-TRD group was not stated. Overall, there were no significant clinical differences between the TRD and non-TRD groups. The tracer was injected while subjects sat resting with eyes open and ears unoccluded. A region of interest (ROI) approach with corrections for multiple comparisons and for whole brain cortical activity (i.e. normalization) showed the amygdala–hippocampal region to be hyperactive in TRD compared with non-TRD patients and controls. There was no significant activity difference between the non-TRD and control groups.

Using PET, Kimbrell et al. measured both absolute and relative rCMRglu in 38 middle-aged, unmedicated (>2 weeks) patients, whose depression was of variable severity and duration, and 37 healthy controls [90]. The patient group was

further subdivided into two subgroups: depressed ($\text{HAM-D}_{28} > 22$; $n=11$) and euthymic ($\text{HAM-D}_{28} < 10$; $n=9$). All subjects were scanned after performing an auditory continuous performance task (CPT) during tracer uptake. A review of retrospective life charts led to a “refractory index” that ranged from 0–100, with higher numbers reflecting greater treatment failures. The depressed group had the following characteristics: $\text{HAM-D}_{28} = 26 \pm 4$ (standard deviation), refractory index 59 ± 27 , and 14 ± 9 previous failed drug trials. In comparison, the euthymic group had $\text{HAM-D}_{28} = 6 \pm 3$, refractory index 16 ± 8 , and 3 ± 2 previous failed drug trials. The authors made several comparisons, but only those relevant to TRD will be reviewed. The refractory index correlated positively with normalized rCMRglu in the left orbital cortex and left precuneus. No significant correlations arose for the absolute data. Of note, the left subgenual cingulate (BA 25) showed a negative correlation between normalized rCMRglu and an “episodes factor” (derived from principal components analysis based upon the number of lifetime depressive episodes and the number of episodes per year). Additionally, this report highlighted that results can differ when using normalized versus absolute rCMRglu measurements.

Using functional MRI, Kumari et al. studied affective processing in TRD as these patients do not respond to the usual approaches and might best reveal dysfunction in circuitry [91]. Based on their earlier work, they hypothesized that TRD patients would have diminished sensitivity to positive stimuli in the medial frontal cortex and either decreased or increased (from anxiety) sensitivity to negative stimuli. The experimental group consisted of six women, aged 36–52 years, with MDD of at least 2 years’ duration who had failed multiple trials using different approaches (SSRIs, MAOIs, TCAs, and ECT). Two patients had had multiple, extensive courses of ECT and were awaiting psychosurgery. The control group consisted of six women, aged 32–55 years. The task paradigm, originally developed by Teasdale et al. [92], consisted of viewing picture–caption pairs and reporting the degree of positive or negative affect they experienced on a 5-point scale after the scan. Picture–caption pairs, each presented on the left and right of the video screen, could be congruent (picture and caption eliciting similarly valenced affect, e.g. positive picture–caption stimulus pair on both sides eliciting positive affect) or incongruent (i.e. reference pictures irrelevant to the caption eliciting neutral affect). Behaviorally, there was a significant effect of valence (positive/negative/reference), but no group (TRD/control) or group \times valence interaction. The imaging results showed that, in TRD, the medial frontal regions, including the rostral right anterior cingulate (BA 24/32), were hypoactive in response to both positive and negative stimuli compared with reference stimuli. The

primary source of this effect was the patients’ increased sensitivity to reference pairs or, equivalently, blunted response to negative pairs. Therefore, the results confirm the primary hypothesis that TRD patients have dysfunction in the anterior cingulate cortex, probably affecting responsiveness to treatment. Whether or not depressed patients who eventually respond have similar changes in this paradigm remains uncertain. The finding converges with extant imaging data on treatment nonresponders (but not necessarily TRD) in unipolar samples showing anterior cingulate hypometabolism when compared with healthy controls (e.g. [13,14,93,94]).

The other comparisons were exploratory rather than hypothesis-driven. Perhaps the most relevant contrast is the comparison of negative picture–caption pairs minus positive picture–caption pairs for patients versus controls. Patients showed a reduced response in the left hippocampus and post-central gyrus (BA 4–6). Each of these reductions was driven by greater activation to positive picture–caption pairs (as compared to the reference stimuli) by controls. In addition, patients had greater responses than controls in the right parahippocampal gyrus (BA 28), left brainstem, left inferior frontal gyrus (BA 47), middle occipital gyrus (BA 19), and right pulvinar. These additional findings were interpreted in several ways:

- Hippocampal dysfunction in TRD whereby negative words arouse controls to retrieve autobiographical memories and, in patients, the inhibition of mnemonic processing of positive words.
- Covert or overt sensorimotor processing of positive words (e.g. smiling) turning on the post-central gyrus, which does not occur in TRD.
- Impaired cerebellar processing of emotive words in TRD (akin to the cerebellar cognitive affective syndrome [95]).
- Hyperactivity in TRD of an extended neural network processing scripts to negative words or attempting to integrate emotion and cognition associated with negative words.

This study was the first to attempt to dissect the abnormal network and associated cognitive operations in TRD.

Mayberg et al. recently published the results from a pilot study of DBS of the subgenual cingulate (BA 25) in a sample of six TRD patients [16]. TRD was defined as a failure of four previous adequate antidepressant trials. Patients had duration of depression > 1 year and a HAM-D_{17} score > 20 . All were receiving multiple medications. By the end of the trial at 6 months, four of six patients met criteria for antidepressant response ($> 50\%$ reduction in baseline HAM-D score). Resting

¹⁵O-water PET scans measuring normalized rCBF in the first five TRD patients were compared with those from five matched controls. Data were analyzed using SPM99. At baseline, patients showed subgenual anterior cingulate hyperactivity and hypoactivity in the prefrontal (BA 9/46), premotor (BA 6), dorsal anterior cingulate (BA 24), and anterior insular cortices, compared with controls (Fig. 4). Three of the five patients were re-scanned at 3 months. Compared with their baseline scan, additional reduction in activity was seen in the VMPFC. This pattern extended further forward (anterior) at 6 months. There was a suggestion that this pattern was similar for responders and nonresponders alike, with the principal difference appearing in the magnitude of the changes. However, too few subjects were involved in order to reach definitive conclusions about treatment versus response specificity.

Functional neuroimaging of rTMS

Repetitive transcranial magnetic stimulation (rTMS) involves the application to the head of multiple, repeated pulses of a magnetic field of approximately 1 T. Current passes through wire loops causing a variable magnetic field, which in turn induces electrical currents within the brain. rTMS has few side effects, unlike ECT which is associated with cognitive problems such as memory loss. However, rTMS remains purely investigational at this time. Several clinical trials have tested the antidepressant efficacy of rTMS with five of six published meta-analyses reporting a significant treatment effect of rTMS in depression [96], though not always specifically in TRD.

A multicenter, parallel design, randomized, controlled trial of 46 patients comparing left prefrontal rTMS with ECT for MDD was recently reported [97]. In this study, patients had failed an average of 2.5 previous adequate medication trials and remained on their medications at entry. ECT was discontinued when an antidepressant response occurred. rTMS (110% motor threshold; 20 trains of 5 s on and 55 s off; 10 Hz; 15 000 pulses) was given over 15 days. The target area was the left PFC at a location approximately 5 cm anterior to the site of optimal motor stimulation of the hand along a parasagittal plane. This location is often termed the mid-dorsolateral prefrontal cortex (MDLPFC). The primary outcome measures were HAM-D₁₇ and remission ($\leq 50\%$ reduction of symptoms). At the end of treatment, the ECT group had significantly lower HAM-D₁₇ scores than did the rTMS group; however, this difference became nonsignificant with continued aggressive management over the 6-month follow-up period. After the end of treatment and before the follow-up period, 59% of patients in the ECT group had entered remission, compared with 17% in the rTMS group. Secondary outcome measures (Brief Psychiatric Rating Scale, Beck Depression, visual analogue mood scales)

were also better for the ECT group compared with the rTMS group, both immediately after the trial and at 6 months. Thus, it appears that ECT is more effective than rTMS, especially in the short term.

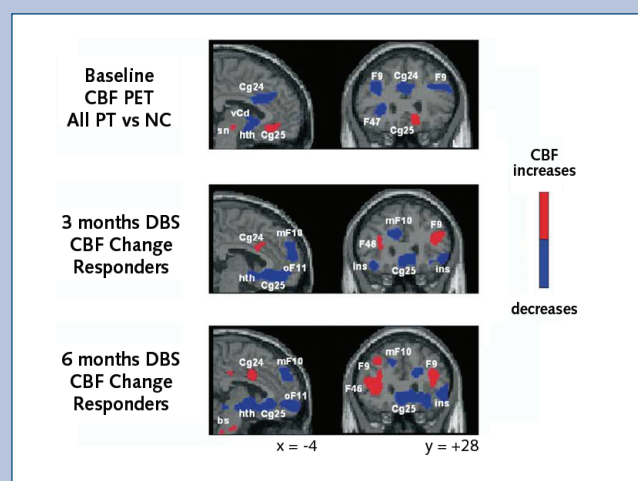
Recently, a US manufacturer became the first to submit an rTMS device for regulatory approval by the Food and Drug Administration (FDA). The submission was based on data comparing the safety and efficacy of the device with ECT in patients with MDD. Of note, several study entry criteria specifically excluded the more severe forms of TRD: current episode duration >3 years, failure of ≥ 4 adequate antidepressant trials, failure to respond to ECT during any previous episode, history of substance abuse within the last year, or history of bipolar disorder. A total of 325 patients from 23 centers were randomized on a double-blind basis to 6 weeks of daily (Monday–Friday) active or sham treatment with left prefrontal stimulation. Unlike most trials of this type, the sham and active device looked and sounded similarly; a frequent sham treatment angles the device away from the skull. Treatment was administered to the left MDLPFC at 120% MT, 4 s on, 26 s off, at a frequency of 10 Hz. Each session lasted approximately 37 minutes. Only hypnotics or anxiolytics were permitted during the trial.

Consistent with past research, this study showed the device to be safe. The primary outcome measure of depression severity, Montgomery–Asperger Depression Rating Scale (MADRS [98]) at 4 weeks, was reduced by 5.6 in the active rTMS group and by 3.5 in the sham treatment group from an approximate initial score of 33 ($p=0.057$). Although the primary outcome did not achieve statistical significance, several secondary measures did. However, the FDA Advisory Panel denied approval. The comparison of rTMS to ECT *vis à vis* relative risk/benefits may have adversely impacted the assessment. To reiterate, rTMS remains investigational at this time and is not approved by the FDA for the treatment of depression.

One possible cause of the weak efficacy of rTMS concerns the location of the coil on the head (typically at left MDLPFC). Given that prefrontal hypometabolism is frequently seen in depression [46], perhaps stimulating precisely over a region of hypofunction identified by neuroimaging (i.e. image-guided) might allow optimal coil placement. However, a recent study reported no improvement in clinical response after image-guided placement [99]. Overall, rTMS appears to have antidepressant effects, but its efficacy is less than that of ECT. In its favor, rTMS carries fewer risks of side effects; therefore, the role of rTMS in TRD, whether adjunctive or maintenance, should be studied further.

The mechanisms by which rTMS ameliorates depression have not yet been determined definitively. In healthy subjects, rTMS acutely induced a coupling of the left DLPFC

Figure 4. Average change in regional cerebral blood flow (rCBF) overlaid on template magnetic resonance images (left, sagittal $x=-4$; right, coronal, $y=+28$). All subjects were on medications and were scanned while resting with eyes closed. Top panel shows the contrast between treatment-resistant depression (TRD) patients and healthy matched controls ($n=5$). Middle panel shows the rCBF change between the scans after 3 months of deep brain stimulation (DBS) compared with baseline ($n=3$). Bottom panel shows similarly the change after 6 months of DBS ($n=3$). Increased rCBF is shown in red and reduced rCBF in blue. Note the baseline hyperactivity in the ventromedial prefrontal cortex (VMPFC) (specifically Brodmann area 25) of TRD patients compared with healthy controls. Note also the progressive decline in metabolism compared with baseline in the VMPFC with ongoing chronic DBS.



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with several regions in the anterior cingulate, demonstrating true functional connectivity [100]. A series of studies by Barrett et al. provide a particularly compelling set of observations [101–103]. In these studies, the investigators sought to determine in healthy subjects how repeated cycles of rapid rTMS modulated cortical activity, as assessed by scanning during a probe of slow rTMS. After a single session of 10-Hz rTMS over the MDLPFC, healthy subjects showed acute changes opposite to those seen after chronic rTMS in depressed patients (i.e. rTMS induction of negative affect rather than an antidepressant effect). Barrett et al. further showed that a speech task sensitive to affect and linked to the anterior cingulate behaviorally demonstrated the induction of a transient negative affect following rTMS. They applied a 10-Hz “conditioning” rTMS before a 1-Hz “probe” rTMS, during which a CBF PET scan was obtained. A positive covariance was seen between rCBF in the left MDLPFC and affect-relevant regions, including the VMPFC (gyrus rectus), perigenual anterior cingulate, insula, parahippocampus,

thalamus, and caudate nucleus. Furthermore, with repeated blocks of conditioning stimulation within an rTMS session, there was a dramatic shift with MDLPFC covarying positively with the left VMPFC (gyrus rectus) and perigenual cingulate cortex, while covarying negatively with the amygdala and a different region of the VMPFC. Recently, both the hemisphere of stimulation and the frequency were varied in a within-subjects design, suggesting a complex interaction of these two variables on rCBF during rTMS that also modulated mood-related regions [104]. Therefore, rTMS in healthy subjects over the left MDLPFC appears to modulate both VMPFC and amygdala neuronal activity, as well as several other regions related to affect and its regulation. However, the precise experimental protocol (side of stimulation, frequency, conditioning versus probe pulses) and analysis method can greatly alter the specific findings.

Several imaging studies of rTMS in MDD have been reported. Nahas et al. conducted a double-blind, placebo-controlled study of rTMS (10 days at 100% MT over the left MDLPFC; 40 repetitions over 20 min of 30 s on with variable rest periods between stimulations; on, stimulation frequency at either 5 Hz or 20 Hz; total 16 000 stimuli for each stimulation frequency) in 16 MDD and seven bipolar depressed patients [105]. Seven were resistant to antidepressants. The authors measured rCBF at 18 min into the last session using ^{99}Tc -bicisate (ethylcysteinate dimer) SPECT while subjects rested with eyes closed. They found increases in rCBF, depending on the frequency of stimulation, in the left DLPFC, left mid-cingulate, and left hippocampus. The VMPFC was activated when comparing active stimulation with baseline condition.

In a HMPAO SPECT study in eight MDD patients, Nadeau et al. reported reductions in VMPFC, anterior cingulate, posterior cingulate, insula, and amygdala activity when images were obtained within 5 days of the final rTMS (10 days; 50 repetitions of 2 s on and 28 s off; 20 Hz; 2000 stimuli; left MDLPFC; arrow task) session [106]. Loo et al. treated 16 patients with MDD and with bipolar depression with rTMS (consecutive days; 90% MT; 15 Hz with 1 s on and 3 s off over 3 min [675 stimuli] or 1 Hz with 1 min on and 6 min off [360 stimuli]; left MDLPFC). Using HMPAO SPECT, they contrasted rCBF either during TMS or during sham stimulation on the preceding day. Changes were dependent on the frequency used; of note, reduced rCBF was recorded in the VMPFC at 15 Hz [107]. In another study, Fugita and Koga observed increased activation in the DLPFC with improvement of depression after rTMS (5 days; single pulse every 6–10 s; five stimuli over four frontal sites on both sides) [108]. Overall, rTMS in the treatment of depression appears to alter activity in both limbic and paralimbic structures, as well as the PFC. Changes in the VMPFC are frequently observed.

Functional neuroimaging in VNS

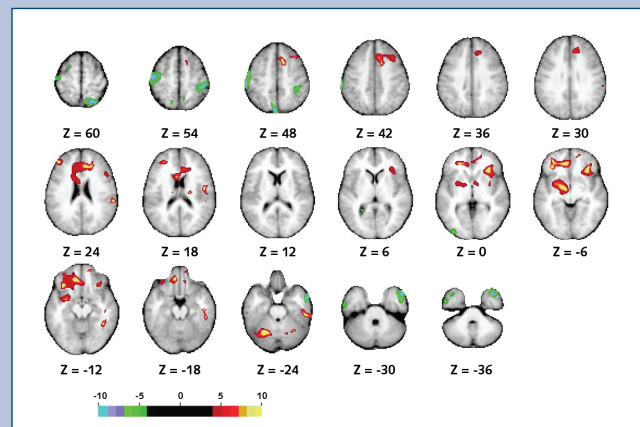
VNS employs a device similar to an externally programmable pacemaker that sends electrical impulses up the left vagus nerve at the neck, through the nucleus of the solitary tract (NTS), and then to widespread brain regions [109–112]. Currently, VNS has two FDA-approved indications: the therapy of medically resistant epilepsy and the adjunctive treatment of TRD. Prior to the initiation of VNS, patients with TRD must have failed four adequate trials of antidepressant treatment. The mode of action of VNS in TRD remains incompletely defined; a recent publication reviewed the plausible mechanisms [113].

The neuroimaging literature on VNS treatment of epilepsy is extensive and beyond the scope of this review (see [114] for review). However, it is clear from this literature that the stimulation parameters (e.g. pulse width [115]), as well as the experimental paradigm, are critical to the results obtained. Because VNS Therapy™ (Cyberonics, Houston, TX, USA) is currently the only FDA-approved adjunctive treatment for TRD, it is not surprising that many of the imaging findings on TRD come from the VNS literature.

Using SPECT, Zobel et al. measured rCBF immediately after a sequence of VNS stimulation in 12 TRD patients for up to 4 weeks of treatment [116]. TRD in this study was defined as severe ($\text{HAM-D}_{24} \geq 20$), chronic (≥ 2 years), recurrent (≥ 4 episodes) depression with failure of at least two adequate trials of antidepressants from different classes or ECT in the current episode. Patients must also have failed to respond to a course of psychotherapy lasting at least 6 weeks. In an analysis using SPM99 and ROIs, the authors identified an extensive network of flow decline involving the amygdala, hippocampus, thalamus, putamen, caudate, brainstem, the subgenual, ventral anterior, posterior, and dorsal anterior cingulate cortices. Flow decline was also seen in the DLPFC and the orbital and ventrolateral PFCs. The only focus of increased flow arose in the middle frontal gyrus.

Using ^{15}O -water PET, Conway et al. studied four, non-epileptic women with TRD treated with adjunctive VNS for 3 weeks [117]. Inclusion criteria were $\text{HAM-D}_{24} \geq 20$, failure of ≥ 2 adequate antidepressant trials during the current episode, and a history of failed psychotherapy of ≥ 6 weeks duration. Prior to imaging, the device was turned off for 30 min. The patients were scanned during the four subsequent blood flow scans in an “off-on-off-on” design. During the “on” scans, 90 s of VNS stimulation was delivered continuously. After the first 60 s, a bolus of the radiotracer was injected. Scanning began 10 s later immediately before tracer injection. These manipulations were designed to optimally capture the rCBF signal from continuous VNS stimulation. Blood flow increased in the orbitofrontal cortex (BA 11, 47), the dorsal (BA 24, 32) and ventral anterior cingulate (BA 32), the superior and inferior frontal gyri, the cerebellum, and the putamen (Fig. 5). Blood

Figure 5. Image of average change in regional cerebral blood flow (rCBF) induced by direct vagus nerve stimulation (VNS) after stereotactic normalization. Four women with treatment-resistant depression underwent 3 weeks of chronic VNS. The device was turned off for 30 min before a 90-s sequence of VNS stimulation was administered. After 60 s of VNS stimulation, a bolus of radiotracer was injected. After another delay of 10 s to enable maximal sensitivity to the direct effects of VNS stimulation, scanning was begun. Increased rCBF is shown in red/yellow and reduced rCBF in blue/green. Note the robust activation in the VMPFC at $Z = -12$.

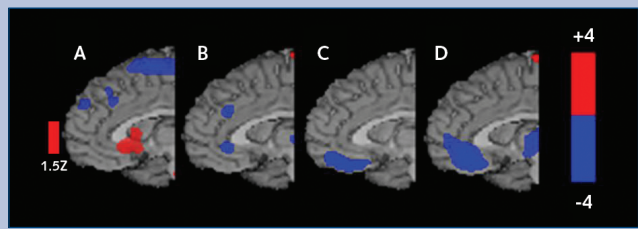


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flow was reduced in the temporal cortex (BA 20, 21), parietal cortex (BA 7, 40), and pre- and post-central gyri.

Using FDG, we recently conducted a study of eight middle-aged TRD subjects enrolled in the manufacturer’s pivotal, double-blind, placebo-controlled trial [110], as well as subsequent follow-up evaluations over 1 year (Pardo et al., unpublished observations). After the first 12 weeks, the study became unblinded and uncontrolled. The imaging component of the study was directed at identifying putative targets of VNS action. The definition of TRD used was that required by the FDA for clinical use of VNS as an adjunctive antidepressant (≥ 4 failed adequate trials). All patients were on polypharmacy and most had comorbid psychiatric conditions. The VNS device was turned off approximately 2 h before imaging to avoid visualizing the direct effects of stimulation described by Conway et al. [117]. Because of the literature reviewed above, we were especially interested in ventral and medial prefrontal changes (i.e. the VMPFC). At baseline (i.e. before activation of the implant), the individual patients showed wide variability with no consistent pattern in subgenual cingulate (BA 25) metabolism compared with healthy controls (data not shown). We compared the changes in rCMRglu over time in each patient. At 3 months, five patients had not had their device activated and there were no significant changes in rCMRglu in this region

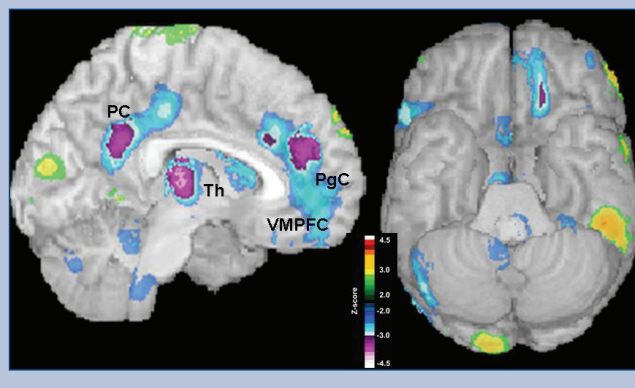
Figure 6. Sequential decline of regional cerebral glucose metabolic rates (rCMRglu) in the ventromedial prefrontal cortex (VMPFC) during chronic vagus nerve stimulation (VNS). All images were averaged after stereotactic normalization, and all sections are sagittal just left of the midline. **A:** Difference image between scans taken after 12 weeks without stimulation (blinded, placebo arm) and baseline scan (n=5). Note that for **A** only, the scale's positive threshold was changed to $Z=+1.5$ to see any differences whether significant or not. The increased rCMRglu at the subgenual cingulate was nonsignificant. **B:** Difference image of rCMRglu of four treatment-resistant depression (TRD) patients comparing a scan taken after 3–6 months of chronic VNS and a baseline scan showing the beginning of hypometabolism in the VMPFC, specifically the perigenual and supragenual anterior cingulate. **C:** Difference image of rCMRglu of four TRD patients comparing a scan taken after 6–9 months of chronic VNS and a baseline scan showing further decline in VMPFC metabolism. **D:** Difference image of rCMRglu of eight TRD patients comparing a scan taken after 9–12 months of chronic VNS and the baseline scan. Note that for **B–D**, the negative Z threshold was -4.0 and is significant. Increased rCBF is shown in red and reduced rCBF in blue.



(Fig. 6A; note the change in threshold from a Z-score of 4.0 to 1.5 to detect any change, no matter how small – this change was actually a slight, nonsignificant increase in activity in the subgenual cingulate). This first comparison is akin to a placebo control because the blind had not yet been broken at 3 months. The more time spent on VNS, the greater the decline in VMPFC metabolism (Fig. 6B–D). Significant decline also occurred in the VMPFC between 6 months and 1 year (Fig. 6C), a finding consistent with the observation that the benefit of VNS increases over the course of at least 1 year, a phenomenon not seen with other treatments [111,112]. At 1 year, none of our patients had remitted and two had responded (~50% reduction in HAM-D score). The modest number of subjects and the limited range of therapeutic responses did not permit determining whether VMPFC hypometabolism occurred in responders only or in both responders and nonresponders. Further research is clearly warranted.

Given the possibility of a rebound phenomenon from turning “off” VNS, we studied four chronic VNS patients while the device was turned “on” according to their usual stimulation

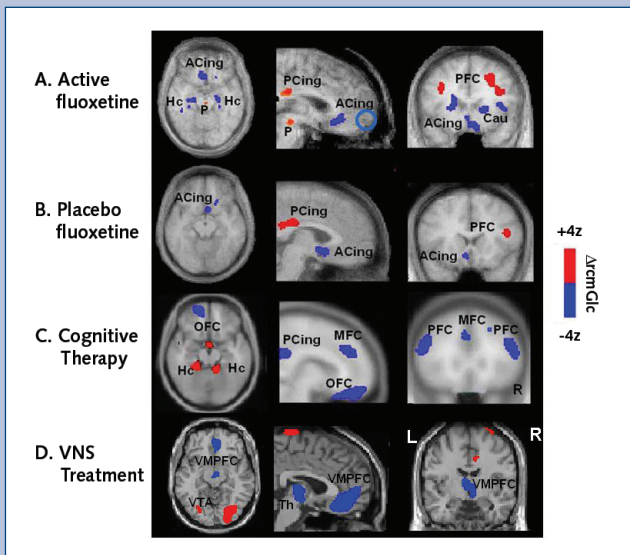
Figure 7. Difference in regional cerebral glucose metabolic rates (rCMRglu) in four chronic treatment-resistant depression patients scanned while the vagus nerve stimulation device was turned “on” (usual parameters: 30 s on, 5 min off) and while the device was turned “off” for 2–6 h. Change in VMPFC was minimal (Z threshold: $-5.0 \leq Z \leq -2.0$). During the on state, hypoactivity is seen in the pregenual cingulate (PgC), posterior cingulate (PC), and thalamus (Th). These structures are known to be anatomically interconnected.



parameters (30 s on; 5 min off) and again while the device was turned off 2–6 h before imaging. Figure 7 shows minimal change in VMPFC activity when comparing the on minus off scans. Turning the device on either reduced activity in the anterior cingulate, posterior cingulate, and dorsomedial thalamic circuit (anatomically well-known thalamocortical and cortico-cortical circuits), or, equivalently, turning the device off increased activity in these regions. The main point is that turning off VNS did not cause any large changes in the VMPFC.

Due to the longer follow-up in our study, these results extend past observations. Moreover, the regions in which we saw robust deactivation correspond with the areas in which Conway et al. saw robust activation from the immediate effects of 60–90 s VNS [117]. Henry et al. also presented convergent data, although from medically refractory epileptics [118]. They timed their 30 s train of stimulation precisely before the arrival of ^{15}O -water into the brain when the procedure is maximally sensitive for detecting change. They showed large activations with acute VNS stimulation in medically refractory epilepsy. After 3 months of chronic stimulation, decreased activation was seen in response to the same 30 s train of VNS stimulation, mainly in cortical regions. As noted above, Zobel et al. also injected tracer immediately after a 30 s train [116]. They reported decreased HMPAO activity in the VMPFC, specifically in the subgenual and ventral anterior cingulate, after only 4 weeks of chronic stimulation. In addition, they reported deactivation in the amygdala, which is densely interconnected with the VMPFC. However, this study used more liberal thresholds for significance, since no corrections were employed for multiple comparisons,

Figure 8. Convergence of ventromedial prefrontal cortex (VMPFC) hypometabolism across multiple treatment modalities. **A:** Change in regional cerebral glucose metabolic rates in responders in a comparison of before and after a fluoxetine trial. The blue circle indicates the approximate location of VMPFC reductions in a paroxetine trial [120]. **B:** Reduced VMPFC metabolism for responders in a placebo arm of a fluoxetine trial. **C:** Reduced VMPFC in a comparison of post- vs. pre-CBT results. **D:** Post- vs. pre-chronic VNS (as in Fig. 6D).



Panels A–C modified with permission from [124]. Panel D from the data presented here.

and is therefore considered exploratory. These data, in addition to ours, suggest that chronic VNS stimulation according to the current standard stimulation parameters results in hypometabolism of the VMPFC. Furthermore, there appears considerable inter-individual variability in the time course of these changes consistent with the wide variability in the timing of clinical response to VNS.

The convergence of the findings in VMPFC are highlighted in Figure 8. Each of the following treatments is associated with decreased VMPFC activity: SSRIs (e.g. fluoxetine [119], paroxetine [120], and sertraline [121]), sleep deprivation [14], CBT [122], DBS [16], and now VNS. However, different treatments recruit somewhat different subregions within this network, as well as other associated brain structures. One mechanism for the decline in VMPFC, at least for the reductions in rCMRglu associated with SSRI treatment, concerns the desensitization of 5HT_{1A} somatodendritic receptors resulting in increased extracellular γ -aminobutyric acid from powerful inhibitory interneurons in the PFC [120]. Additionally, serotonin release inhibits the PFC. The potential mechanism(s) for changes associated with DBS, VNS, sleep deprivation, or CBT remain more nebulous.

How might reducing activity in VMPFC ameliorate depression? In one study, the degree of negative affect in healthy control volunteers while resting with eyes closed correlated highly with activity in the subgenual anterior cingulate (BA 25 [123]). To the extent that pathological emotion in depression relates to negative affect and to homologous circuitry, the subgenual cingulate might be predicted to show hyperactivity in depression. In fact, some literature shows basal hyperactivity of subgenual cingulate in unipolar depression in both treatment-responsive depression and TRD [46,16], although basal hypoactivity in the subgenual region has also been reported [121]. Reduction of subgenual activity might lead to reduced negative affect. This explanation is clearly an over-simplification but provides a framework for testable hypotheses.

Conclusion

The work reviewed in this article leaves two essential questions only partially answered. Firstly, is TRD a distinct type of depression that will ultimately yield imaging-based surrogate markers, essential for clinical use of these expensive technologies? There does not appear to be a consensus yet. At this time, we believe this possibility unlikely and probably simplistic, but only time will tell. TRD samples contain multiple types of depression besides unipolar; often included are patients with bipolar I depression, bipolar II depression, double depression, and multiple other psychiatric comorbidities including personality disorders. After all, TRD by definition requires failure of multiple treatments that all affect the brain. Studies of TRD patients have yet to identify genetically homogeneous groups that will likely affect therapeutic response. However, imaging technologies are advancing rapidly with increasing resolution permitting the detection of previously unseen changes.

Secondly, can we make sense of the bewildering array of neural circuits reported in different studies? The convergence in the VMPFC data across different treatment modalities and laboratories appears striking. Treatments for depression generally reduce the metabolism of the VMPFC, suggesting this may be a final common pathway to recovery. However, each treatment engages different circuitry and different subregions of the VMPFC, and it remains unclear how to view the VMPFC given its highly inter-connected nature, yet highly compartmentalized connections to subcortical structures. Should it be viewed as a whole, integrated unit or as a conglomeration of distinct entities that happen to be in proximity?

In conclusion, the research role of neuroimaging in TRD at this time is paramount. Although there are no clinical indications to use neuroimaging in neuropsychiatric disorders other than in special situations for the evaluation of dementia, the case presented here may provide some indication of future potential.

Functional neuroimaging has already made considerable progress in defining components of the relevant circuitry. Both rTMS and VNS impact upon this circuitry, although the value of these two new modalities in the management of TRD remains to be seen. Psychiatry is poised to make major advances in the next decade both clinically and scientifically through the application of new functional imaging technologies, thereby offering hope for TRD patients.

Acknowledgments

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Psychiatric Disorders and the Risk of Coronary Heart Disease

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Depression, anxiety, and schizophrenia are amongst the psychiatric disorders that have been linked to coronary heart disease (CHD). Despite abundant research, a causal association between depression and CHD has yet to be confirmed. Depression is associated with an adverse prognosis in CHD but meta-analyses and negative results from intervention trials suggest this may be the result of reverse causality. Depression is common in CHD patients and should be treated, but this has not been demonstrated to improve prognosis of CHD. Depression may be linked to the development of new CHD in healthy populations, but the contribution of other emotions, such as anxiety and personality, is unclear and the role of underlying undiagnosed CHD needs more evaluation. Anxiety is not a proven risk factor for CHD, in either etiological or prognostic studies. Schizophrenic patients have an increased risk of CHD, possibly related to lifestyle, behavior, or use of antipsychotic medications. *Depression: Mind and Body* 2007;3(2):71–5.

This review will consider the published evidence for the hypotheses that depression, anxiety, and schizophrenia are independent risk factors for coronary heart disease (CHD). In particular, it will evaluate:

- The quality of the available studies.
- Whether these disorders act as etiological risk factors, leading to the development of CHD in healthy populations, and/or as prognostic risk factors, associated with an adverse course in CHD patients.
- The extent to which any associations are independent of other CHD risk factors, such as smoking, lack of exercise, and poor diet.
- The extent to which associations might be the result of reverse causality, i.e. the psychiatric disorder or symptoms are caused by underlying CHD.
- Whether the effect appears to be reversible, i.e. whether treating the psychiatric condition removes the CHD risk.
- The likely mechanisms involved.
- The nature and severity of the disorder associated with an increased risk of CHD.

Depression

The association between depression and CHD has been extensively studied in recent years, with numerous well-designed, longitudinal, population-based studies published. Many have reported positive associations between depressive symptoms and both the occurrence of new CHD (etiological studies) and an adverse prognosis in established CHD (prognostic studies). Recent meta-analyses have estimated that depression is associated with a 60–80% increased risk of CHD in etiological [1,2,61] and a 70–140% increased risk in prognostic studies [3,4,61]. Although many authors consider depression to be a proven cardiac risk factor, questions remain concerning the nature of this association that need to be resolved before it can be accepted as causal [5,6].

Definition of depression

A wide range of instruments have been used to diagnose or define depression, from single questions or symptom scales to clinical diagnostic categories; hence, the definition of depression used within a single meta-analysis varies considerably. It is clear that mild symptoms short of clinical depression have been associated with an increased risk of CHD in both etiological and prognostic studies. Evidence of a dose–response effect has been seen in etiological studies, with clinically assessed, and probably more severe, depression leading to higher risk [2,61], although this has not been demonstrated in prognostic studies [3,4].

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Independence of effect from CHD risk factors

Many etiological studies control for recognized CHD risk factors, such as health behaviors, blood pressure, and cholesterol levels, and the reduction in the observed risk of future CHD associated with depression after such adjustment is often small [7–11,61]. However, this control is often incomplete, with time-dependent covariates only rarely used [10]. Furthermore, adjusted results are often not reported in studies with weaker unadjusted associations, so that the estimates of adjusted effects in meta-analyses are biased upwards [61]. Other meta-analyses of etiological studies have combined unadjusted and adjusted estimates in their models [3].

Frequently, prognostic studies inadequately control for CHD risk factors, with a similar bias in which studies report adjustments. In addition, adjustment in prognostic studies controls for severity of disease, and thus it is not possible from the available data to estimate the contribution of risk factors, rather than disease severity, to the observed associations. However, recent estimates in prognostic studies suggest a role for smoking and lack of exercise in the associations between depression and CHD [12,13].

On the available evidence, the effect of depression on CHD does not appear to be mediated by established CHD risk factors but there is a need to standardize covariate control to address this fully [5]. Individual patient data meta-analyses are required to standardize both the control of covariates and the definition of depression in order to get a more accurate estimate of the independent effect of depression on CHD risk [14].

Reverse causality by underlying CHD

The role of underlying CHD severity is an important issue in prognostic studies. The observed association between depression and an adverse prognosis could result from patients with more severe CHD at baseline reporting more depressive symptoms than patients with less severe disease. Barth et al. showed a modest reduction in effect after adjustment for a combination of risk factors and disease severity markers [3]. However, in another recent meta-analysis, adjustment for CHD severity at baseline, including a measure of left ventricular function, reduced the estimate of the effect of depression by approximately 50% [61]. Given that such adjustments have only been reported in studies with stronger unadjusted results, this suggests an important role for reverse causality in the observed associations. Other authors have argued similarly that more detailed adjustment for disease severity is required before depression can be accepted as an independent risk factor for mortality in myocardial infarction (MI) patients [15–17].

The extent to which underlying undiagnosed CHD is involved in associations between depression and CHD in

etiological studies is unknown. It is possible that depression arises in response to the early signs of CHD or to the inflammatory processes involved in plaque rupture [18], which may account for the observed associations. Similar mechanisms have been suggested as an explanation for the link between vital exhaustion and CHD events [19]. Some studies have found that only a recent increase in depressive scores is associated with future CHD, which may represent reverse causality [20,21], but other etiological studies have reported an increased CHD risk associated with depression lasting for several decades, which is inconsistent with such endogeneity [10]. Even if depression actively influences the pathogenesis of CHD rather than resulting from the progression of atherosclerotic plaques, it is unclear whether depression acts as a long-term atherogenic risk factor, leading to the development of atherosclerotic plaques, or as an acceleration factor, promoting the activation and rupture of established plaques. More detailed studies with data on CHD stage and duration of depressive symptoms are required [18,22,23].

Effect of treating depression on CHD risk

Randomized, controlled trials on the treatment of depression with both psychological and pharmacological interventions in post-MI patients have failed to improve CHD prognosis despite improving depression status. In SADHART (the Sertraline Antidepressant Heart Attack Randomized Trial), sertraline was shown to be both safe, with no adverse effect on left ventricular ejection fraction, and more effective than placebo in reducing depressive symptoms in post-MI patients with major depression. The incidence of adverse cardiac events, including death, was lower in the treated group but the difference did not reach statistical significance as the trial was underpowered for adverse events [24]. The ENRICHD (Enhancing Recovery in Coronary Heart Disease) trial compared the effect of a psychosocial intervention with usual care in a mixed group of post-MI patients with depression and/or perceived low social support. The psychosocial intervention was cognitive behavior therapy, with antidepressants (sertraline was the first choice drug) prescribed for more severely depressed patients. In the intervention group, depressive symptoms were reduced but there was no reduction in mortality or recurrent non-fatal MI rates [25]. A subsequent *post hoc* analysis showed that depressed patients taking selective serotonin reuptake inhibitors (SSRIs), whether in the intervention group or not, had a lower risk of death or recurrent MI [26]. Another *post hoc* analysis from ENRICHD showed that the trial intervention improved prognosis in white men but not in women or men from other ethnic groups [27].

Despite these subsequent analyses, an improvement in prognosis after treating post-MI depression has not been

demonstrated. The evidence is strongest for SSRI antidepressants improving the prognosis of such patients, but these results need to be confirmed in future trials. However, the existing data indicate that treating depressed post-MI patients with SSRIs is safe and effective in reducing depression. The use of tricyclic antidepressants (TCAs) is not recommended in CHD patients [28].

The fact that improving depressive symptoms did not improve prognosis in the ENRICH trial raises important questions regarding whether the effect of depression on CHD is reversible and the nature of the psychological risk factor implicated [6]. These findings are consistent with the hypothesis that depression arises as a response to more severe CHD. However, they should not detract from the need to identify and treat depressive illness in CHD populations to relieve the distress inherent in depression.

There have been no intervention studies looking at the effect of treating depression on the risk of future CHD in healthy populations; therefore, it is unclear whether any effect of depression on the pathogenesis of CHD is reversible. Antidepressant use has been studied in observational, etiological studies and found to predict events [8,29], but it is difficult to separate the effect of the drug from the effect of the underlying depression. There is some suggestion that TCAs are cardiotoxic in overdose and may increase the risk of future CHD events [6]. They are not recommended as first-line drug therapy for depression [30]. SSRI use has not been associated with an increased risk of future CHD [6].

Other social and psychosocial factors

Apart from mediation by cardiac risk factors and reverse causality, another potential explanation for the observed associations between depression and CHD is confounding by other social factors, such as low social status, psychosocial characteristics, or personality traits. Some, but by no means all, studies adjust for education or social class, but the impact of adjusting only for social class on depression as a CHD risk factor has not been quantified. Adjustment for other social measures, such as social support, is much less frequent.

In addition, the extent to which the effect of depressive symptoms on CHD risk is independent from other negative emotions, such as anxiety, or personality traits has been poorly investigated. Some authors argue that much of the observed association can be accounted for by enduring personality type and high negative affectivity being detected by depressive symptom scales rather than fluctuating mood [31]. The few studies that have attempted to control for other negative emotions have had contradictory results. Frasure-Smith and Lesperance found that depression was

a predictor of cardiac mortality over and above the effect of negative affectivity [32]. In etiological studies, some authors have found that the features of depression were not significant when anxiety was adjusted for [22,33], whereas Kubzansky et al. found that anxiety, anger, and depression were each associated with CHD risk [34].

Mechanism

Despite extensive research efforts, the mechanism underlying the increased risk of CHD associated with depression remains unclear. Conventional CHD risk factors do not appear to explain the associations. Other candidate mechanisms include increased activity of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system, reduced heart rate variability, increased platelet activation, and inflammatory pathways [18,35–37]. These potential pathways have often been studied in small, cross-sectional studies of clinically depressed patients, rather than in population-based studies of participants with depressive features who have been shown to be at an increased risk of CHD. Where population-based data are available within prognostic studies, the results have been more supportive of arrhythmic rather than ischemic mechanisms [23,38,39].

Anxiety

Longitudinal, population-based studies of anxiety as a CHD risk factor are sparse compared with the abundant literature on depression. No meta-analyses have been published, and the narrative reviews of the association between anxiety and CHD have been varied in their conclusions, partly due to different inclusion criteria [40–43]. Some reviews have admitted cross-sectional studies and studies restricted to patient populations (hence lacking internal controls), and other reviews have included studies using a generalized psychological distress score as an exposure variable.

Within the etiological literature, evidence is strongest for a link between phobic anxiety and future sudden cardiac death [44,45]. However, there are no recent confirmatory reports and a later study by Haines et al., with follow-up extended to 20 years, was negative for phobic anxiety but positive for obsessional neurosis and somatic complaints [33]. In a recent study in women, phobic anxiety was significantly associated with sudden cardiac death only in unadjusted analyses [46]. The Normative Aging Study has produced several papers using different anxiety measures in relation to CHD endpoints (Minnesota Multiphasic Personality Index [34], Cornell Medical Index [47], and a worry scale [48]) with generally positive results, but these results from a single study population are not truly independent. In some of the papers, generalized anxiety

measures were only significant in unadjusted analyses, suggesting that anxiety may act through established CHD risk factors [47,49].

In addition, anxiety has been examined as a prognostic factor, often in the same studies as depression. Reviewers have concluded that the evidence does not support the hypothesis that anxiety is a prognostic risk factor [40,42]. Given this lack of association, the role of reverse causality has not been investigated. No intervention studies have been designed to test the reversibility of the effect by treating anxiety in CHD patients.

The mechanism by which anxiety may have an effect on CHD has not been established and the available data suffer similar problems of generalizability as the literature investigating the mechanisms of depression. The data on the relationship between anxiety and heart rate variability are the most compelling, particularly given the findings regarding sudden cardiac death [50,51]. It is not possible to assess the presence of dose–response effects in the anxiety literature due to imprecision in the definition of exposure variables. None of the existing studies provide an estimate of the effect size of clinical anxiety disorders and many use instruments that assess personality rather than current emotional state.

This raises questions about the nature of psychological risk factors being measured and crucially whether it is really possible to separate out the anxiety and depression aspects of affective disturbance. Anxiety research has suffered from the recent attention to depression and many depression symptom scores will also measure anxiety. As discussed with regard to depression, the separation of different negative emotions and the extent to which personality rather than an acute emotional disturbance underlie the observed effects is unresolved.

Schizophrenia

The increased mortality rate seen in schizophrenia patients compared with the general population is a matter of concern, and the risk of CHD has been considered within this context. Most of the available studies have compared the mortality of a defined patient population with national rates and calculated standardized mortality ratios, rather than comparing the mortality of schizophrenia patients with unaffected participants within the same study population. The fact that such patient population studies have limited capacity to control for confounding and selection bias is an issue, although this is less problematic for a severe illness such as schizophrenia. Meta-analyses of these studies have suggested a modestly raised risk of cardiovascular death in schizophrenia patients (including hypertensive deaths as well as CHD) with a standardized mortality ratio of 110 [52,53].

Larger standardized mortality ratios have been estimated for cerebrovascular, respiratory, and digestive diseases than for cardiovascular disease (CVD), indicating a lack of specificity in the effect of schizophrenia on CHD. However, population-based studies with internal controls have also reported an increased risk of CHD death in male schizophrenia patients [54] and of CVD mortality [55], but in the latter study increased mortality was related to arrhythmia rather than MI.

Although not a specific association, CHD is an important cause of increased mortality in schizophrenia patients. The reasons for this increase in mortality rate are unclear. Adverse health behaviors and lifestyle are likely to contribute [56]. Furthermore, there have been concerns since the 1980s about the increased risk of sudden cardiac death due to antipsychotic drugs [57]. More recent data indicate that atypical antipsychotics may be associated with weight gain, diabetes, the metabolic syndrome, and lipid dysregulation, and thus increase the risk of CHD [58]. One study of increased mortality in schizophrenia patients found a graded relationship with the number of neuroleptics prescribed [59]. Reports that the treatment of CHD is suboptimal in schizophrenia patients are plausible [60], but there have been no prognostic studies of the long-term outcome of such patients.

Conclusion

Despite abundant research, much remains unexplained in the relationship between psychiatric disorders and the pathogenesis of CHD. A causal association between depression and CHD has not yet been demonstrated. The effect of adjusting for CHD severity on the association between depression and adverse prognosis in CHD suggests that the observed correlations may be the result of reverse causality. The lack of a dose–response effect and negative results from intervention trials support this explanation. Depression is common in CHD patients and should be treated, but this has not been demonstrated to improve the prognosis of CHD. Depressive features may increase the risk of future CHD in healthy populations, but the mechanism involved is unclear and it has not been demonstrated that the effect of depression is independent from the effect of other negative emotions and personality traits. The role of underlying undiagnosed CHD requires further evaluation.

Anxiety is not a proven risk factor for CHD, in either etiological or prognostic studies. An association between phobic anxiety and sudden cardiac death has been reported in men, but for generalized anxiety the data are inadequate to consider elements that might strengthen the argument for causality, such as reverse causation, independence, and dose–response.

Schizophrenia patients have an increased risk of CHD, possibly related to lifestyle and behavior, and there are concerns about the contribution of antipsychotic medication to this risk. Cardiovascular risk factors and physical health should therefore be carefully monitored in these patients.

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Dr Nicholson has no relevant financial relationships to disclose.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Paul Ballas and Po Wang

EPIDEMIOLOGY

A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up

Widom CS, DuMont K, Czaja SJ.

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This study revealed that childhood sexual abuse did not result in increased risk of developing major depressive disorder (MDD), while neglect increased the risk of current MDD. In addition, lifetime development of MDD was increased in subjects who had been physically abused or those who had experienced multiple forms of abuse. This suggests it would be prudent to screen abused and neglected children for signs of depression.

Although there has been substantial research on the psychiatric consequences of childhood abuse, few prospective longitudinal studies have focused on the specific relationship between childhood abuse and the development of major depressive disorder (MDD). The present authors conducted a prospective assessment of risk for developing depression in children with documented abuse or neglect compared with a control group of children followed into adulthood. Information was also gathered to assess the effect of different kinds of abuse on the risk of developing major depressive disorder (MDD), as well as the timing of the development of depression and other psychiatric disorders.

The data came from a prospective cohort study in which children who had been victimized before the age of 12 years were identified through court records from 1967–1971. Information on a comparison group was gathered from elementary school records from the same period on children who were matched to the abused subjects by sex, ethnicity, age, and family social class. Typically, two control subjects were assigned for each abused child. Control subjects who reported abuse were excluded from the study. Certain abused children could not be matched because they were born outside the

country, went to elementary schools that had closed since 1971, information of the date of birth of the abused child was missing, or the school the child went to was not integrated at the time and a control subject was not found.

The second phase of the study involved a 2-h interview at a mean of 22.3 years after the initial data points. These interviews included rating scales and questionnaires on psychiatric disorders. Subjects and interviewers were blinded to the purpose of the study. Of 1575 subjects initially screened, 1196 (75.9%) were located and interviewed. Of those who were not interviewed, 268 could not be located, 60 refused to participate, eight were incapable of being interviewed, and 43 had died prior to the interview. There were no demographic differences between the original and follow-up samples.

MDD was assessed using the National Institute of Mental Health Diagnostic and Statistical Manual, Third Edition revised (DSM-III-R). The authors assessed several other symptoms associated with depression in the DSM-III-R, including thoughts of death, reduced ability to concentrate, feelings of worthlessness, fatigue, psychomotor retardation, insomnia, loss of appetite, lack of interest in activities, and depressed mood. Other DSM-III-R psychiatric disorders assessed included dysthymia, drug or alcohol dependence and/or abuse, post-traumatic stress disorder, and generalized anxiety disorder.

The study revealed that approximately one-quarter of neglected and/or abused subjects had MDD compared with one of five subjects in the control group, although this difference did not reach statistical significance. Analysis of specific types of abuse revealed that subjects with a history of physical abuse or multiple forms of neglect and abuse were at an increased risk of developing MDD (odds ratio [OR] 1.72; $p=0.06$)

Neglected children showed an increased risk of developing current depression (within the past year of the interview) compared with the other subgroups of the abused and control subjects.

The mean age of the onset of depression was earlier in abused and neglected subjects compared with controls

(mean 18.2 vs. 20.8 years). With regard to comorbid disorders, 96.4% of neglected or abused subjects with MDD, 83.4% of control subjects, and 91.3% of subjects overall had at least one additional DSM-III-R symptom. Of those subjects who had been abused and neglected and had lifetime MDD, 86.4% had an additional psychiatric disorder compared with 72.2% of the matched controls. Furthermore, 79.4% of subjects who had been abused and neglected and had current MDD had an additional psychiatric diagnosis compared with 69.1% of matched controls. In general, there was no difference between the depressed subject in the neglected and abused groups and the controls with regard to the timing of the comorbidity of other psychiatric illness, with two exceptions. Abused or neglected subjects were more likely than controls to have MDD prior to the onset of substance abuse and/or dependence (40.4% vs. 17.4%; $p < 0.01$); and control subjects were more likely than the neglected and/or abused subjects to have either alcohol dependence and/or abuse (58.2% vs. 40.2%; $p = 0.04$) or drug dependence and/or abuse (76.1% vs. 46.8%; $p < 0.001$).

The data presented here come from the first prospective long-term study on the risk of MDD in neglected and abused children followed into adulthood. The findings suggest an increased risk of developing MDD as a result of childhood abuse and neglect. These findings may be limited by the fact that the original and follow-up samples represented a population at the lower end of the socioeconomic scale.

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Hospitalization for depression is associated with an increased risk for myocardial infarction not explained by lifestyle, lipids, coagulation, and inflammation: the SHEEP study

Janszky I, Ahlbom A, Hallqvist J et al.

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This population-based, case-control study assessed the potential risk for myocardial infarction (MI) as a result of a hospitalization for depression. After controlling for several confounding factors the data revealed that patients who had been hospitalized for depression had an odds ratio for an acute MI of 2.9 (1.8–4.9). Therefore, depression may increase risk for an acute MI, even after many other risk factors for heart disease have been considered.

Several research studies have suggested that depression may increase the risk of coronary heart disease. However, much

of the data is limited by follow-up assessments of <10 years' duration and inadequate control for confounding factors. The current study explored the relationship between the risk of a first myocardial infarction (MI) and depression in subjects with an exposure window of 26 years.

Data were collected as part of the Stockholm Heart Epidemiology Program (SHEEP), which includes data from every Swedish citizen in Stockholm county aged 45–70 years with no prior history of MI. Females cases were identified by data from 1992–1994 and males by data from 1992–1993. Data on subjects were collected from Swedish national and Stockholm county registries, as well as the departments of internal and emergency medicine.

The criteria for an acute MI included electrocardiogram findings, cardiac enzyme blood levels, and symptoms described in case histories. Patients meeting ≥ 2 of these criteria, or those with autopsy findings consistent with MI, were placed in the acute MI group. Control subjects were selected from similar registries.

Depressed individuals, identified through the Swedish healthcare system, were defined as those who had a hospitalization discharge diagnosis of neurotic or psychotic depression based on the International Classification of Diseases, Eighth Revision. All 4069 participants were screened for covariants with a health examination and questionnaires. Thus, information was gathered on several possible confounding variables including diabetes, sleep problems, lipid abnormalities, physical inactivity, obesity, smoking, alcohol use, socioeconomic condition, and hypertension.

The study yielded data on 2339 control subjects and 1799 patients who had suffered an MI. In all, 69 subjects (22 controls and 47 MI subjects) had either psychotic or neurotic depression, 19 (four controls and 15 MI) had psychotic depression, and 54 (19 controls and 35 MI) had neurotic depression. The median time between first hospitalization for depression and acute MI was 15 years and 2 months. The odds ratio (OR) for being in the acute MI category with a hospital discharge diagnosis of any form of depression was 2.9, while the OR for psychotic depression specifically was 5.0. Notably, increased hospitalizations for depression were associated with higher ORs for acute MI. The OR for one hospitalization was 2.5 compared with 6.8 for patients with >3 hospitalizations.

Lifestyle-related covariants and socioeconomic position had only moderate influences on the OR for depression. Furthermore, MI patients had similar risks of developing acute MI regardless of whether their first hospitalization was before or after the median time between the first hospitalization for depression and MI (15 years and 2 months). Within 28 days of an MI, depression was found to increase the risk for death. Specifically, 15 of the 47 acute MI patients who had

previously been hospitalized with depression died during this period compared with 358 of the 1752 acute MI subjects not previously hospitalized for depression (OR 1.7).

This data and others from previously published research suggest that hospitalization for depression carries a relative risk for an acute MI similar to that of smoking. Evidence from this study suggests recurrent hospitalizations increase the risk further, and depression may be associated with increased mortality due to MI. Additionally, psychotic forms of depression appear to increase the risk of an acute MI more than neurotic depression.

This study has two limiting factors. First, defining depression based on hospitalization may have yielded a low sensitivity as many subjects in the non-depressed group may have had mild to moderate depression that did not lead to a hospitalization. Second, certain data of covariants were not available for subjects who died within 28 days of MI, thus the effects of this data on the relationship between depression and MI are not known.

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Diurnal variation in regional brain glucose metabolism in depression

Germain A, Nofzinger E, Meltzer C et al.

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The authors compared variation between regional cerebral metabolic rate of glucose (rCMRglc) and mood throughout the day in depressed patients and control subjects. The results suggest that depressed patients have different rCMRglc compared with non-depressed people. Mood elevation in depressed patients in the evening occurs with an increase in specific metabolic patterns in the brain and could be a form of normalization of neural systems.

These authors aimed to compare variations in regional cerebral metabolic rate of glucose (rCMRglc) and mood throughout the day in depressed patients and non-depressed control subjects. They used data from a larger project examining relative regional glucose metabolism during sleep and wakefulness. In these patients, rCMRglc was assessed using ¹⁸F-fluorodeoxyglucose positron emission tomography ([¹⁸F]-FDG PET) during morning and evening wakefulness. Additionally, subjects underwent screening brain magnetic resonance imaging scans before the PET studies to identify any pathology.

The study included 12 depressed patients and 13 controls. Depressed patients were identified with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Third Edition revised (SCID) and each had a score

of ≥ 15 on a 25-item Hamilton Rating Scale for Depression (HAM-D). None of the depressed subjects were on antidepressant medication and all were additionally assessed with the Raskin Severity of Depression and Mania Scale, the Pittsburgh Sleep Quality Index, and the Circadian Type Questionnaire (CTQ), which includes a subscale of preference for morningness and eveningness.

On the first night of the study, all subjects underwent an initial polysomnographic (PSG) study at their usual sleep times. Additional baseline sleep assessments occurred on the second night. On the third day, [¹⁸F]-FDG PET scans were carried out 2–4 h after awakening and again the same evening while the subjects were being monitored by electroencephalograms. Prior to PET scans, participants completed several mood and rating scales, including either the Likert scales from the Profiles of Mood States assessment or the 100 mm Visual Analogue Scale.

The results showed that depressed subjects had mean HAM-D scores of 24.42 compared with 0.3 in control subjects. Depressed patients all experienced a recurrence of MDD, with an average duration of the current episode of 50.73 weeks. Additionally, patients had a history of an average of 4.22 prior depressive episodes. One depressed subject had obvious changes in mood throughout the day based on HAM-D scores, five subjects had infrequent and mild diurnal variation in mood, and six had no change. None of the control subjects had any significant diurnal change in mood.

Self-reported, subjective, diurnal mood ratings worsened in one depressed patient, remained unchanged in five, and improved in six. Means scores of the morningness subscale of the CTQ did not differ between the nine depressed and 11 control subjects for whom the data were available. However, repeated-measure analyses of variance (ANOVA) showed a significant group \times time of day effect on mood scales. Control subjects had lower mood ratings in the evening than in the morning, while depressed subjects showed an improvement in mood in the evening. There was no significant difference between groups with regards to time spent awake in the morning or evening, and no correlation between mood scales and glucose metabolism in either group.

In depressed subjects two specific brain regions had relatively significant greater rCMRglc during evening wakefulness than in the morning. The first included the right superior temporal gyrus, parahippocampal gyrus, cerebellum, and hippocampus and the second included parts of the midline medial prefrontal cortex, the left medial temporal region, and the cerebellum.

Furthermore, ANOVA of group \times time of day interaction revealed that the left locus coeruleus and the right midbrain reticular formation showed smaller increases in relative

rCMRglc in the morning and evening in depressed subjects compared with controls.

Statistical analysis in depressed patients revealed two areas in the brain that had a greater increase in relative rCMRglc in morning and evening compared with the control group. Small-volume correction analyses showed a greater increase in the right inferior parietal cortex and interaction analysis showed an increase in the area that includes the superior and inferior parietal cortices and the central postcentral gyrus.

Post hoc analysis revealed several differences between the groups at different times during the day. Compared with controls, depressed subjects had lower rCMRglc during morning wakefulness in several regions of the brain, including the superior and middle frontal gyrus. Furthermore, in the morning assessments depressed subjects had lower rCMRglc in the right dorsolateral prefrontal cortex.

Compared with healthy subjects, depressed participants had increased rCMRglc in the right inferior occipital gyrus and in a second cluster that included the insula, uncus, and left parahippocampal and lingual gyri. Additionally, depressed subjects had lower rCMRglc during the evening in several regions, including the medial dorsal anterior cingulate cortex and medial frontal cortex.

Volume of interest analysis showed that depressed subjects had greater rCMRglc in the morning compared with healthy subjects in several areas, including the amygdala and mid-anterior insula. Elevated relative rCMGglc was seen in depressed subjects in the evening in a large region that included the parahippocampal gyri, hippocampus, and cerebellum.

The data revealed that mood ratings in depressed patients improved over the course of the day in comparison with healthy controls, and was associated with changes in morning to evening variations in rCMRglc. The authors assert that this study is the first to suggest depression may cause diurnal variation in regional brain metabolism.

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Cost-effectiveness of systematic depression treatment among people with diabetes mellitus

Simon GE, Katon WJ, Lin EH et al.

Arch Gen Psychiatry 2007;**64**:65–72.

The results of this robust randomized, controlled trial indicate that screening for and treating depression in patients with diabetes mellitus is cost-effective from a medical and psychiatric perspective.

Depression is commonly observed in patients with diabetes mellitus, increasing treatment costs in those with this

comorbidity. Treating depression in these patients would be expected to decrease the mental health morbidity, but whether such a psychiatric intervention would decrease overall medical costs needs to be examined. The present study investigated the cost-effectiveness of a systematic depression treatment program in patients with diabetes from a consortium of nine prepaid primary care clinics in Washington state and Idaho, USA.

Of 500 000 members, 9063 were identified by computer records as having diabetes mellitus. After two stages of depression screening with the Patient Health Questionnaire followed by the Hopkins Symptom Checklist, 329 completed enrollment in the trial. Subjects were randomized to a multi-stage intervention for depression or treatment as usual. The two groups were generally similar in terms of demographic variables. In the multi-stage intervention, nurses first offered patient-selected pharmacotherapy (new antidepressant or current antidepressant dose adjustment) or psychotherapy. After 12 weeks of inadequate response, patients received combination therapy, such that psychotherapy was added to existing antidepressant treatment, or antidepressants were added to ongoing psychotherapy. After another 12 weeks of inadequate response, patients were referred to a psychiatrist. Antidepressant selection, dosing, and criteria for adjustment were based on other treatment-trial algorithms. Outcome measures included the number of days "depression-free", the overall cost of outpatient medical and psychiatric care, and the cost of administering the study, all assessed over the study's 2-year duration.

The intervention group had lower depression scores throughout the 2 years of the study. By the end of the first year, this group had experienced 20 more depression-free days than the usual-treatment group, and this difference was extended by a further 33 days during the second year of the study. Hemoglobin A_{1c} levels did not differ between the two groups. Excluding the monetary cost of depression, the total fiscal cost for the intervention group over 2 years was estimated to be US\$314 less than that for the usual-treatment group. Specifically, the intervention group had higher depression treatment costs as expected, but these were more than offset by lower medical treatment costs during the study. In fact, most of the depression treatment costs were incurred in the first year, but the benefits due to decreased medical treatment costs began in the first year and increased into the second year. If a monetary amount could be applied to the improved mood in the intervention group, the cost-effectiveness of the depression intervention would have been even more dramatic. Clearly, depression screening and treatment would be a cost-effective standard of care for primary care settings.

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Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care

Dayan J, Creveuil C, Marks MN et al.
Psychosom Med 2006;**68**:938–46.

This prospective cohort study explored the relationship between antenatal depression and anxiety and preterm birth due to preterm premature rupture of membranes or preterm labor. Women with high depression scores had a higher rate of spontaneous preterm birth than non-depressed women, even after adjusting for confounding variables. There were no significant differences in anxiety scores between groups.

Past research has reached differing conclusions with regard to prenatal depression and preterm birth. Several studies suggest an association, while others show no relationship between these two clinical phenomena. The present authors applied multiple logistical regression analysis to previously published data to examine the relationship between spontaneous preterm birth and prenatal depression and anxiety symptoms.

The study included 721 women aged 18–45 years at 20–28 weeks' gestation. Forty subjects (5.9%) were excluded for not completing all the questionnaires. Depressive symptoms were assessed by the Edinburgh Postnatal Depression Scale (EPDS), with a score of ≥ 14 indicating antenatal depression. The EPDS is the only depression rating scale validated for use during pregnancy and the postnatal period. State and trait anxiety symptoms were assessed by the Spielberger State–Trait Anxiety Inventory. Outcome variables included delivery before 37 weeks' gestation due to either preterm pre-labor rupture of membranes or preterm labor.

Potential confounding factors included parity, pre-pregnancy body mass index, previous preterm birth, and various complications of current pregnancy, including urinary tract infections, polyhydramnios, and vaginal bleeding.

Depressed women were more likely to be a victim of partner violence and have a lower level of education. In addition, these women were more likely to be hospitalized in the second trimester and were more likely to attend a “high stress” prenatal visit at the beginning of the study. The prenatal visit included either an ultrasound examination, admittance examination prior to hospitalization, or amniocentesis. Higher trait and state anxiety was reported in subjects who were hospitalized in the second trimester, those who had gestational hypertension, and those who attended a high stress prenatal visit. A slightly higher prevalence of state anxiety was found in women with vaginal or cervical infections. Subjects with high occupation

and education levels were less likely to have trait anxiety. Spontaneous preterm delivery was associated with several variables, including hospitalization during the second trimester, gestational age at enrollment, polyhydramnios, and vaginal and cervical infections. Furthermore, the rate of spontaneous preterm birth was greater in women who were depressed during pregnancy than non-depressed women (9.7% vs. 4.0%; $p=0.023$). Multivariate analysis revealed that depression was the only psychological factor associated with spontaneous preterm birth.

The data presented in this study suggest that women with depression may be at higher risk of preterm birth.

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White-matter integrity predicts stroop performance in patients with geriatric depression

Murphy CF, Gunning-Dixon FM, Hoptman MJ et al.
Biol Psychiatry 2007;**61**:1007–10.

Using a whole-brain, voxel-based methodology (therefore, excluding *a priori* assumptions of regions of interest), areas of reduced fractional anisotropy (a measure of white-matter structural integrity) correlated with reduced performance on the Stroop color word interference task (a measure of executive dysfunction) in frontostriatal-limbic white-matter tracts in patients with major depressive disorder.

Depression has been termed a reversible dementia, particularly referring to the executive functional impairment common in older adult patients with major depressive disorder (MDD). Neurocognitive testing of frontal lobe function correlates with severity of depression in some studies, and structural imaging has shown dysfunction in corresponding frontostriatal-limbic circuits. In a previous study conducted by the authors of the present article [1], poor performance on the Stroop color word interference task (CWI) was correlated with compromised white-matter integrity in a predetermined region of interest, namely, the white matter lateral to the anterior cingulate gyrus. The aim of the present study was to determine whether the functional–structural correlations would extend to other brain areas.

Using a whole-brain, voxel-based methodology, 51 older adults (mean age 70 years) with MDD completed the Stroop CWI and underwent diffusion tensor imaging (DTI). Fractional anisotropy (FA), a measure of water diffusion capacity and direction that reflects white matter integrity, was determined by DTI. FA was calculated for the whole

brain and mapped to standardized Talairach space. FA was then correlated voxel by voxel to Stroop CWI scores. After adjustment for age and correlations between FA and the color naming score of the Stroop test, Stroop CWI performance was found to be significantly related to FA in frontostriatal-limbic white-matter regions, including the left anterior cingulate and left insula. The results of this whole-brain, voxel-based study therefore confirms that structural defects in frontostriatal-limbic white-matter tracts are correlated with executive dysfunction in patients with MDD.

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The costs and benefits of enhanced depression care to employers

Wang PS, Patrick A, Avorn J et al.

Arch Gen Psychiatry 2006;63:1345–53.

This study examined the financial impact to employers and society of increased depression screening and care in workers. On average, increased depression screening and management had a US\$19 976 incremental cost-effectiveness ratio per quality-adjusted life year compared with usual care. Employers received a benefit of US\$2895 after 5 years. The results suggest that increased screening and treatment of depression may be cost-beneficial to employers and society.

A substantial amount of research suggests that increased screening and treatment of depression is cost-effective to society as a whole. However, the widespread uptake of treatment programs has not been forthcoming. There have been no studies to date on the effect of depression screening and treatment programs on productivity in working populations. The present authors attempted to estimate the cost-effectiveness of depression care programs from both societal and employer perspectives.

A state-transition Markov model was constructed to explore this issue using a computer program. The model comprised six disease states: depressed in or not in treatment, recovered in or not in treatment, never depressed, and dead. Additionally, the depression intervention arm included with or without care management states. Intervention involved a one-time screening for depression, with treatment available for those who were found to be depressed. Treatment was defined as a visit to a physician and initiation of a selective serotonin reuptake inhibitor. Distribution between the six disease states was

based on prevalence data for depression, number in treatment, and number in recovery. Movements between alive and dead states every 3 months were based on probabilities from the clinical literature.

Additional published data were used to estimate transitional probabilities (e.g. mortality rates), management, visits, and hospitalization costs. Societal perspective analyses were used to calculate variables including quality-adjusted life expectancies. Employer's perspective analyses were used to assess monetary benefits and costs for 5 years, including productivity losses due to depression, costs of intervention, and lost work time due to obtaining treatment.

The societal perspective analysis revealed that the cost of an employer-based depression screen and telephone-based management program for depression was US\$3699, but this resulted in 18.785 discounted quality-adjusted life years (QALYs). Furthermore, care management increased life expectancy from 21.9337 to 21.9343 life-years. The average lifetime cost per person was US\$39.8 more for the intervention component compared with usual care.

The employment perspective analysis revealed that in the first year, the intervention group cost employers US\$601 per 1000 workers. However, this figure is almost offset by the benefits of treatment, such as increased productivity. In the second year, the intervention saved employers US\$4631 per 1000 workers as a result of effects on, for example, absenteeism and employee turnover. The subsequent 3–5 years had a modest cost to employees. However, over 5 years the intervention resulted in US\$2895 in savings per 1000 workers compared with usual care.

This study suggests that the one-time depression screening and treatment program used by the authors would result in improvement in QALYs at costs typically covered by employee-sponsored medical insurance programs.

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Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women

Kennedy SE, Koeppe RA, Young EA et al.

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The μ -opioid receptor system differs in depressed women during a neutral task and a sadness induction positron emission tomography task compared with matched healthy controls, particularly in areas that overlap stress response and emotion circuits.

Evidence suggests that the stress response is linked to the pathophysiology of mood disorders. The

hypothalamic–pituitary–adrenal axis is generally thought to mediate this interaction. The μ -opioid receptor (μ -OR) system is densely distributed in brain regions containing both stress response and emotion circuits, such as the striatopallidal pathway, anterior cingulate cortex, and prefrontal cortex. Thus, investigation of the μ -OR system may lead to important insights into the relationship between the stress response and mood disorders. The authors of the present study used positron emission tomography (PET) and the ^{11}C -labeled carfentanil to measure μ -OR binding potential (μ -OR-BP) in 14 women with major depressive disorder (MDD) and 14 individually matched healthy controls, first in a neutral state and then during a sadness induction task. All subjects completed the Positive and Negative Affectivity Scale (PANAS) at baseline and after completion of each of the experimental conditions. MDD patients were subsequently treated for 10 weeks with fluoxetine.

In the neutral state, μ -OR-BP in the right posterior thalamus was significantly lower in patients compared with controls ($p < 0.01$ after correction for multiple comparisons), and μ -OR-BP in this region was higher in those who responded to fluoxetine treatment than in non-responders. There was a significant negative correlation between right thalamic μ -OR-BP and plasma corticotropin levels ($r = -0.58$; $p < 0.05$). Although a lower μ -OR-BP was seen in the left posterior thalamus of patients compared with controls, this difference was not significant. Again, patients who responded to fluoxetine treatment had higher μ -OR-BP in this region compared with the non-responders. The authors found that μ -OR-BP in the left posterior thalamus was negatively correlated with plasma corticotropin levels ($r = -0.61$; $p < 0.05$) and with plasma cortisol levels ($r = -0.58$; $p < 0.05$). During sustained sadness, patients showed significant decreases in regional (left inferior temporal cortex) μ -OR-BP, which were correlated with the degree of sadness induced ($r = 0.67$; $p < 0.01$), i.e. patients with lower μ -OR-BP had higher PANAS negative affect scores. In contrast, controls had significant increases in regional (rostral anterior cingulate) μ -OR-BP, indicating deactivation of μ -opioid neurotransmission, with the degree of deactivation correlated with the degree of negative affect induction ($r = 0.62$; $p = 0.02$), i.e. controls with greater μ -OR-BP had higher PANAS negative affect scores. Non-responders to a 10-week course fluoxetine showed increases in μ -opioid system activation in this region in the sad state, while responders displayed responses more closely related to those of controls (deactivation).

Overall, during sadness induction, the μ -OR radiotracer probe revealed differences in many regions that overlap stress and emotion circuits between MDD patients and controls. The μ -OR neurotransmission system may thus

represent an important avenue for research into the relationship between stress response and mood disorders.

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Relationship between depression severity entry criteria and antidepressant clinical trial outcomes

Khan A, Schwartz K, Kolts R et al.

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This study showed that higher pre-randomization scores on the Hamilton Rating Scale for Depression at the entrance of 51 antidepressant trials were not associated with more favorable outcomes.

Several criticisms have been made about the design of most randomized, placebo-controlled trials of antidepressant medications. One suggestion is that using higher scores on the Hamilton Rating Scale for Depression (HAM-D) to define depression would result in more positive results and less placebo effect. Another concern is that the dosing schedules used in most trials have a clinical effect; specifically, those trials that allow a flexible dosing schedule may maximize the benefit of the medication being tested and again reduce the benefit seen in placebo subjects. Increasing sample size in trials has also been suggested to result in more clear benefits of antidepressant medication. The present authors attempted to address these concerns in a study examining the effects of symptom severity, trial length, and dosing schedule on the results of 51 previously published trials. These trials assessed 10 different antidepressant medications and included 11 270 depressed subjects.

The authors collected data from the Summary Basis of Approval reports of the US Food and Drug Administration (FDA) for 10 antidepressant medications approved for use from 1985–2004. These reports are generated by the FDA as part of the New Drug Application for each medication. Information was collected on the dosing schedule, number of patients in each trial, length of trial, and pre-randomization HAM-D scores. Trials were placed into the following categories based on the HAM-D scores at study entry: “low” for subjects scoring ≥ 14 on the HAM-D₁₇, “moderate–low” for a score of ≥ 18 on the HAM-D₁₇, “moderate–high” for a score of ≥ 20 on the HAM-D₂₁, and “high” for subjects with a score of ≥ 20 on the HAM-D₁₇. Several statistical analyses were used to examine outcomes and other variables between the groups.

Of the 11 270 depressed subjects, 5466 were receiving the antidepressant under investigation, 1817 had received

an active competitor, and 3987 had received a placebo. Of the 51 trials included in the study, 10 were in the high category, 14 in the moderate–high group, 20 in the moderate–low group, and seven in the low category. Average trial lengths in the high, moderate–high, moderate–low, and low categories were 6.8, 6.7, 5.6, and 8.6 weeks, respectively. The four categories differed in the number using flexible dosage schedules, number of subjects, and trial outcomes. Flexible dosing was used in 95% of trials in the moderate–low category, but the other groups did not differ in the number of trials using fixed versus flexible dosing. Antidepressant treatment arms showed superiority over placebo in 20% of trials in the high category, 50% in both moderate–high and moderate–low categories, and 44.4% in the low category. The difference between the high category and the other three categories combined reached statistical significance (20% vs 49%; $p=0.04$).

The findings of this study suggest that higher pre-randomization HAM-D scores for depressed subjects in the 51 antidepressant trials examined was not associated with more favorable outcomes.

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Are stress-induced cortisol changes during pregnancy associated with postpartum depressive symptoms?

Nierop A, Bratsikas A, Zimmermann R et al. *Psychosom Med* 2006;**68**:931–7.

The results of this prospective study suggest that higher psychosocial and cortisol reactivity in response to stress may help identify pregnant women who will go on to develop post partum depression.

Post partum depression has been the subject of a great deal of research, and multiple studies have been published on the relationship between the hypothalamic–pituitary–adrenal (HPA) axis and depressive disorders. However, little has been published on the role of basal cortisol levels and HPA reactivity in pregnancy and their relationship to post partum depression. This study assessed whether psychobiological stress reactivity during pregnancy is predictive of the development of post partum depression symptoms.

The authors recruited 57 healthy women who were pregnant for the first time. The women were screened for psychiatric disorders using Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID-I) and the SCID-II. The Trier Social Stress Test (TSST) has previously been shown to include

cardiovascular and endocrine responses in 70–80% of subjects. All subjects gave saliva samples before and after participating in the TSST and additional samples were taken at 10, 20, 30, 45, and 60 min after the test. Following delivery, the women underwent a semi-structured interview and within 13 days post partum were assessed for various psychological and physiological variables. A score of ≥ 10 on the Edinburgh Postnatal Depression Scale (EPDS) was used as the cut-off point for post partum depression screening. The Multi-dimensional Mood Questionnaire (MDBF) was used to assess psychological stress factors and the State–Trait Anxiety Inventory was used to assess state and trait anxiety. Stress susceptibility was determined using the Measure for Assessment of General Stress Susceptibility scale, a 36 item, six subscale questionnaire. Psychopathology was assessed with the Symptom-Checklist-90-Revised (SCL90-R). Birth outcomes examined included birth weight, mode of delivery, pregnancy complications, and gestational age at delivery. Specific birth complications included preterm delivery, second- and third-degree perineal rupture, secondary cesarean section, and blood loss of >500 mL.

Based on postpartum EPDS scores, 28.07% of participants ($n=16$) were categorized as “probable cases” while the remaining 71.93% ($n=41$) were considered “probable non-cases”. The groups did not differ with regards to complications during pregnancy or birth, birth weight, gestational length, or mode of delivery. Repeated-measure analyses of variance (ANOVAs) revealed that compared with the probable non-case group, the probable case group had higher cortisol responses to the TSST. However, one-way ANOVA with the area under the response curve calculated revealed no difference for salivary cortisol between groups.

The TSST resulted in decreased mood scores on the MDBF. Statistical analysis of the data revealed a time and group effect, with the highest values in the probable non-case subjects and the lowest values in the probable case subjects. Furthermore, probable cases were shown to have higher state and trait anxiety and stress susceptibility scores.

This study is the first to compare physiological and psychological reactivity to stress during pregnancy among healthy women. Pregnant women with higher depression scores had increased state anxiety, greater decrease in mood, and increased hormonal response to stress than women with lower depression scores. Therefore, it may be possible to identify a population of women who are at higher risk of developing postpartum depression by assessing their physical and psychological response to stress during pregnancy.

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CLINICAL PRACTICE

Overweight and obesity affect treatment response in major depression

Kloiber S, Ising M, Reppermund S et al.

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Overweight and obesity are commonly comorbid with mood disorders, such as major depressive disorder and bipolar disorders, and obesity has been shown to have a negative effect on treatment response in patients with these disorders.

Overweight and obesity are common health problems in the general population, particularly in the Western world. Psychiatric patients are particularly at risk of being overweight or obese. Both excessive weight and psychiatric illness have negative effects on morbidity and mortality rates. There is high comorbidity between mood disorders (major depressive disorder [MDD] and bipolar disorders) and obesity. The present authors investigated the effect of overweight and obesity on the treatment of MDD in 408 inpatients who participated in the Munich Antidepressant Response Signature project.

Subjects were assessed weekly for 5 weeks during treatment with therapeutic doses of antidepressants chosen by their doctor. As seen in previous studies [1–3], MDD patients had a higher body mass index (BMI) than healthy controls without mood or anxiety disorders (25.05 vs. 24.42 kg/m²; $p < 0.01$). Patients with a low BMI (<18.5 kg/m²) or with a low depression score, as measured by the Hamilton Rating Scale for Depression (HAM-D), were excluded from the analysis of treatment response. Patients with a higher BMI (≥ 25 kg/m²) had a significantly slower response to antidepressants than those with a normal BMI (≥ 18.5 to <25 kg/m²), based on linear mixed-effects modeling analysis. To investigate the effect of weight on treatment response, patients were divided into three categories: normal weight (BMI ≥ 18.5 to <25 kg/m²), overweight (BMI ≥ 25 to ≥ 30 kg/m²), and obese (BMI > 30 kg/m²). The results revealed a trend towards a slower response with higher BMI.

One potential confounder was that depression severity was lower in patients with a BMI of ≥ 25 kg/m² than in those with a BMI of ≥ 18.5 to <25 kg/m². This may have been partly because loss of appetite and weight loss are symptoms of depression, which would have led to lower weights for the more severely depressed patients. When these weight, appetite, and insomnia symptoms, all not present in atypical depression, were excluded, depression severity was similar.

Both obesity and MDD have independent negative effects on morbidity and mortality rates. These factors also

interact with one another such that patients with mood disorders have higher rates of obesity, and obesity adversely affects the treatment response of patients with MDD. These treatment interactions are also observed in patients with bipolar disorders [4]. Together, these results point to the need for mental health providers to simultaneously address both metabolic and psychiatric illness in obese patients with mood disorders.

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Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review

Ruhe HG, Huyser J, Swinkels JA et al.

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This study suggested that a switch between any of the antidepressant classes may be legitimate as no clear benefit has been shown for switching from one class of antidepressant to another.

Previously published research suggests just 50–60% of patients with major depressive disorder (MDD) respond to the first antidepressant given. Various guidelines recommend dose escalation, augmentation with a second medication that is not an antidepressant, or switching from one antidepressant to another. Little systematic research has focused on specific recommendations for non-responders. The present authors attempted to systematically review available published research on switching antidepressants after patients fail to respond to a selective serotonin reuptake inhibitor (SSRI). They also reviewed data from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, which consists of four sequential levels of treatment (levels I–IV).

Using Cochrane methodology, the authors conducted a meta-analysis of switching to a second SSRI or switching to a serotonin norepinephrine reuptake inhibitor (SNRI) after a first SSRI was used. Randomized and open studies in which at least 50% of participants used SSRIs were included. Studies that described switching from tricyclic antidepressants (TCAs) to SSRIs were excluded. Literature searches were conducted using PsychInfo, Medline, Embase,

and Cinahl databases. The authors independently screened articles for design and emphasis on switching antidepressant treatment after an SSRI, collecting data on efficacy and tolerability. The primary efficacy data comprised intention-to-treat (ITT) based percentages of subjects responding or in remission. The Hamilton Rating Scale for Depression was utilized if multiple scales were available in the studies. Tolerability was assessed by overall dropout rate and dropout rate due to side effects of medication. Since there was a paucity of randomized controlled trials, data were pooled from just three studies that compared the switching to a second SSRI or to venlafaxine, an SNRI.

In all, 31 studies were selected for review, seven of which were open studies investigating switching to a second SSRI. Response rates to a second SSRI in non-controlled studies ranged 42–58%, but studies in which participants were not tolerant of the first SSRI had response rates ranging 56–72%. Dropout rates due to side effects were 0–10% in the SSRI-intolerant studies and 5–21% in initial non-responder studies. Response rates from three randomized controlled trials ranged 26.7–71.1%, remission rates were 17.6–52.1%, and dropout rates due to side effects were 4.8–21.0%.

In order to investigate the results of switching from a TCA to an SSRI or *vice versa*, the authors screened two randomized controlled trials studies that examined the response from switching from a TCA to an SSRI, four open studies that examined the response of switching from an SSRI to a TCA, and the STAR*D level III study. Among the findings the authors noted a 16.5–48.5% response rate for switching from a SSRI to a TCA, with lower rates reported in subjects who were more treatment resistant.

In order to investigate the results of switching from an SSRI to a dual-acting agent, 13 switch studies were examined, including four randomized controlled trials and the STAR*D trial. Overall, these studies showed 28–50% response rates for switching to venlafaxine, nefazodone, and mirtazapine, again with reduced response in those with treatment-resistant depression. Pooling of data showed a slight clinically equivocal advantage in remission rate for venlafaxine compared with the other SSRIs (number needed to treat, 13).

In order to investigate the results of switching from an SSRI to bupropion and reboxetine, the authors examined two open studies and one randomized controlled trial, including the STAR*D level II study. Switching to bupropion resulted in a 26.1–34.6% remission rate compared with up to 45.3% on switching to reboxetine.

The authors identified several studies that examined switching to monoamine oxidase-A inhibitors, including two randomized studies and one randomized controlled trial

from the STAR*D level IV study. The STAR*D trial showed lower emission rates for tranylcypromine (6.9%) and combination treatments (13.7%) in subjects who had previously received an SSRI. Additionally, no significant difference was found in the response rates between tranylcypromine/venlafaxine and mirtazapine.

This study systematically reviewed available literature on switching strategies in MDD patients who do not sufficiently respond to SSRI medication. The results suggest that switching to any class of antidepressant results in an approximately 50% rate of response. The findings of this review are limited by the fact that much of the data came from non-controlled open-label studies, which are more likely to yield positive outcomes than blinded studies.

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Acupuncture for depression: a randomized controlled trial

Allen JJ, Schnyer RN, Chambers AS et al.
J Clin Psychiatry 2006;**67**:1665–73.

Acupuncture, as a complementary and alternative medicine technique, may be the preferred intervention for many individuals with major depressive disorder. However, this study – the largest randomized, controlled study of acupuncture for depression performed to date – found only modest efficacy compared with a wait-list condition (waiting without intervention), and no difference in efficacy compared with a control acupuncture treatment that targeted points not specific for depression treatment.

Many mental healthcare patients have a preference for complementary and alternative medicine (CAM), including acupuncture, for the treatment of major depressive disorder (MDD). Although some reports suggest that acupuncture provides a benefit, only one of these trials involving just 38 women, used a rigorous, double-blind, randomized study design [1]. To replicate their prior findings with a larger sample, Allen and colleagues conducted a study of 151 patients with MDD randomized to receive 8 weeks of either monotherapy with traditional Chinese medicine (TCM)-style acupuncture targeted for depression, an active control of monotherapy with TCM-style acupuncture using points not specific for depression, or a wait-list condition (waiting without intervention). Each intervention involved a total of 12 sessions of acupuncture, and patients were monitored with the Hamilton Rating Scale for Depression (HAM-D). At the end of the 8 weeks, all three groups were offered the active TCM-style acupuncture specific for depression for a further 8 weeks.

Both acupuncture-treated groups (depression-specific and non-specific) showed significantly greater changes in HAM-D than the wait-list group. However, the depression-specific and non-specific acupuncture treatment groups did not differ in terms of response, with 22% and 39% meeting the response criteria, respectively, compared with 17% of the wait-list group. Acupuncture was well tolerated, with only 13% of patients discontinuing before completion of the randomized phase of the trial. Adverse events were not systematically collected in the wait-list group.

Subjects were recruited without reference to the use of CAM treatments for depression, increasing the ability to apply these results to the general population and minimizing the selection bias of patients preferring and anticipating improvement with CAM treatments. The non-specific acupuncture technique was devised to use legitimate acupuncture techniques to relieve symptoms, without specifically targeting symptoms related to depression. Those who scored patients on the HAM-D were blind to the treatment; however, the acupuncturists were obviously aware of the techniques they were employing, although they were blind to the study design and hypothesis.

Overall, the response rate was only modest, suggesting that acupuncture is not supported as a monotherapy intervention for MDD. In addition, acupuncture specifically targeted for depression did not provide a superior benefit compared with a non-specific acupuncture intervention, bringing into question the validity of the acupuncture's biophysiological theory for depression.

1. The efficacy of acupuncture in the treatment of major depression in women. *Psychol Sci* 1998;**9**:397–401.

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Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms

Sanacora G, Kendell SF, Levin Y et al. *Biol Psychiatry* 2007;**61**:822–5.

In this open study on patients with major depressive disorder, riluzole, a medication with anti-glutamatergic effects, decreased depression and anxiety scores.

Emerging evidence has suggested a glutamatergic component to mood disorders. Thus, certain anti-glutamatergic medications may have antidepressant effects. The present authors examined the antidepressant effects of riluzole, a medication approved by the US Food and Drug

Administration for amyotrophic lateral sclerosis, which is known to decrease glutamate neurotransmission.

In this open study, 10 patients with major depressive disorder (MDD) who had failed to respond to at least 6 weeks of antidepressant treatment received add-on treatment with riluzole (50 mg twice daily) for up to 12 weeks. Hamilton Rating Scale for Depression (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) scores were rated weekly. Linear mixed-model analysis revealed that both HAM-D and HAM-A scores decreased significantly during the study, even by the end of the first week, and continuing throughout the study period. Four patients showed a decrease in HAM-D score of $\geq 50\%$ by week 6. The most frequent adverse event was fatigue, requiring dosage adjustment in two subjects. Although hepatotoxicity is a known concern, there were no significant changes in hepatic enzymes in any of the subjects during the study.

These data, suggesting a potential antidepressant benefit of riluzole, are consistent with other studies that have reported antidepressant (MDD and bipolar disorder) and anxiolytic effects [1,2]. Neuroprotection is a developing theory to explain the mechanism of action of antidepressants. As glutamate is associated with excitotoxicity, the anti-depressant effects of anti-glutamatergic medications are consistent with this theory.

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2. Zarate CA Jr, Payne JL, Quiroz J et al. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 2004;**161**:171–4.

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Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment

Chen CH, Ridler K, Suckling J et al.

Biol Psychiatry 2007;[Advance online publication].

Anterior cingulate cortex grey matter density and functional magnetic resonance imaging task activation may predict response to fluoxetine in patients with major depressive disorder.

Depressive disorders are common conditions with many effective treatments available. However, up to 50% of patients will not achieve remission, despite overall response rates of 70–80% to antidepressant medications. Identification of patients most likely to respond to a specific treatment may improve treatment outcomes. The present authors investigated pretreatment structural and functional neuroimaging correlates of response to 8 weeks of fluoxetine treatment in 17 patients with major depressive disorder.

Overall, treatment decreased mean Hamilton Rating Scale for Depression (HAM-D) scores by 63%. Structural imaging data, obtained using a 1.5-T scanner, were analyzed statistically by correlating baseline grey matter density maps with changes in depression severity. Baseline depression severity was negatively correlated with frontal grey matter, particularly the dorsal, prefrontal, and anterior mid-cingulate cortices. Greater grey matter density in the anterior cingulate cortex, insula, and right temporoparietal cortex was associated with response to fluoxetine.

Functional magnetic resonance images (fMRIs) were obtained using an event-related paradigm while patients viewed Ekman series faces showing varying degrees of sadness. In this investigation, only those areas of association derived from the structural analysis were evaluated. Greater activation of the pregenual anterior cingulate cortex predicted a faster response to fluoxetine.

The anterior cingulate cortex can be divided into histologically and functionally distinct regions that include the subgenual and pregenual regions. The Mayberg group recently investigated deep brain stimulation targeted at the subgenual anterior cingulate cortex for treatment of patients with refractory depression [1]. This current study replicates previous findings indicating that the pregenual anterior cingulate cortex may have important therapeutic implications [2]. Both regions have been implicated as areas that may predict and possibly mediate treatment response.

1. Mayberg HS, Lozano AM, Voon V et al. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45:651–60.
2. Mayberg HS, Brannan SK, Mahurin RK et al. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 1997;8:1057–61.

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Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE)

Kellner CH, Knapp RG, Petrides G et al. *Arch Gen Psychiatry* 2006;63:1337–44.

This paper reports on the first randomized, controlled study of active continuation treatments following acute electroconvulsive therapy remission. Continuation electroconvulsive therapy was found to have similar relapse, remission, and early study discontinuation rates to medication.

Electroconvulsive therapy (ECT) is the most efficacious treatment for acute depressive disorders. However, in the absence of some form of continuation therapy, relapse rates

after acute treatment are as high as 80% at 6 months. The two main continuation therapies currently in use are medication or ongoing ECT. In the present study, the authors systematically investigated the efficacy of these two options.

In five academic centers, 531 patients with major depressive disorder received ECT (bitemporal electrode placement with stimulus dosing of 1.5 times the titrated seizure threshold determined at first treatment) three times per week until remission. Of the patients with a documented medication history, only 43% had undergone at least one prior adequate antidepressant trial. Of the 64% who met the remission criteria, 60% maintained remission for 1 week prior to randomization, leaving 201 patients divided equally between the continuation ECT (cECT) and continuation medications (cMED) groups. In the cECT group, patients received ECT weekly for 4 weeks, biweekly for 8 weeks, and monthly for 2 months. Subjects were followed for 6 months. In the cMED group, patients received nortriptyline and lithium at doses calculated to achieve steady-state levels of 125 ng/mL and 0.7 mEq/L, respectively, for 6 months. The primary outcome measure was time to relapse.

The cECT and cMED groups had similar times to relapse (9.1 weeks vs. 6.7 weeks, respectively). In the cECT group, 37% relapsed and 46% maintained remission, while the remaining patients discontinued the study early. Similarly, in the cMED group, 32% relapsed and 46% maintained remission. In both groups, rates of relapse were better than those for patients without any continuation treatment. On an interesting note, cognitive scores were comparable in the two groups during the study.

This study does not address the common clinical practice of combining cECT with other medications or using more tolerable antidepressants, such as selective serotonin reuptake inhibitors (given the high discontinuation rates in this study). Routine clinical practice has a more individualized ECT schedule, with the flexibility to have a short acute course of ECT during the continuation phase of ECT. Antidepressant choices would also be more flexible, as clinicians would tend to choose antidepressants for the continuation phase that had not previously been ineffective in acute treatment. Nevertheless, this is the first study to compare different active strategies for the maintenance of remission after acute ECT. Although efficacy was similar, differences in the adverse effect profiles of the two treatments (headache and memory for cECT; anticholinergic effects, tremors, and sedation for cMED) may influence patient choice.

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CARDIOVASCULAR RISK

Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes

Frasure-Smith N, Lespérance F, Irwin MR et al.
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In this study, the presence of depression and higher levels of inflammatory markers predicted an earlier time to a major adverse cardiac event in men after an acute coronary syndrome. However, the effect of depression on cardiac risk is not completely mediated by inflammatory mechanisms. Furthermore, the contributions of depression and inflammation to cardiac risk are not additive.

The hypothetical basis for an association between major depressive disorder (MDD) and coronary artery disease (CAD) includes an inflammatory mechanism that may involve interleukin-6 (IL-6) and other markers of inflammation. In this study, Frasure-Smith and colleagues, who previously reported these important findings [1], further explore the relationships between MDD, CAD, and the inflammatory response.

Depressive symptoms (measured by the Beck Depression Inventory II [BDI-II]) and inflammatory markers (IL-6, C-reactive protein [CRP], and soluble intercellular adhesion molecule [sICAM-1]) were measured in patients 2 months after an index acute coronary syndrome. Of 1815 potential subjects who attended two Montreal (QC, Canada) hospitals and were invited to participate in the ESCAPE (Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions) study, 741 patients completed the assessments and had their data included in the analysis. Associations between baseline measures and the occurrence of major adverse cardiac events (MACEs; including cardiac death, survived myocardial infarction, survived cardiac arrest, and non-elective revascularization), assessed at 6-month intervals over 2 years, were investigated. Follow-up was outstanding, with only six patients lost.

Overall, 27% of the subjects had BDI-II scores ≥ 14 , consistent with at least mild-to-moderate levels of depression. Replicating prior findings, MACEs were associated with both continuous BDI-II scores (hazard ratio [HR] 1.20 per standard deviation increase, 95% confidence interval [CI] 1.01–1.42; $p=0.041$) and categorically elevated scores (≥ 14) for BDI-II (HR 1.74, 95% CI 1.17–2.59; $p=0.007$). When the authors investigated interactions between sex and depression in predicting MACEs, there was evidence for an association between elevated BDI-II scores

and risk of MACEs in men ($p=0.004$), but not in women ($p=0.85$). Risk analysis was therefore confined to men.

Men with a BDI-II score of ≥ 14 had higher CRP and sICAM-1 levels, and a greater number of other cardiac risk factors (sedentary lifestyle, smoking, higher fasting triglycerides, higher fasting glucose), but not IL-6 levels. Even after adjusting for relevant covariates, a BDI-II score of ≥ 14 remained a significant predictor of MACEs (HR 1.72, 95% CI 1.07–2.77; $p=0.024$), in agreement with other studies. Additionally, both high levels of CRP and sICAM-1, but not IL-6, were associated with earlier time to first MACE. In a model combining these major risk factors, having either high BDI-II or high CRP was associated with an increased risk of MACEs; however, the risk did not appear to be additive, i.e. high BDI-II and high CRP did not have any higher risk than either factor alone. Furthermore, some patients with a high BDI-II score without high CRP had an increased risk of MACE.

This study suggests that the prognostic impact of depression on cardiac risk is not completely explained by inflammatory mechanisms. The MDD–CAD–inflammatory response relationship needs to be explored further in women (see review of the paper by Kling et al. below).

1. Lespérance F, Frasure-Smith N, Theroux P et al. The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. *Am J Psychiatry* 2004;161:271–7.

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Sustained low-grade pro-inflammatory state in unmedicated, remitted women with major depressive disorder as evidenced by elevated serum levels of the acute phase proteins C-reactive protein and serum amyloid A

Kling MA, Alesci S, Csako G et al.
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Plasma levels of the inflammatory markers C-reactive protein and serum amyloid A are elevated in euthymic women with major depressive disorder compared with matched healthy controls. This suggests a pro-inflammatory state as a common pathophysiological pathway in depressive disorders and coronary artery disease.

Patients with major depressive disorder (MDD) have an independently increased risk of coronary artery disease (CAD), and the presence of depression in patients with recent major cardiac events increases their risk of subsequent cardiac events. The present study investigated the pro-inflammatory state theory, one of the more prominent theories put forward to explain these associations.

The authors measured the common inflammatory markers serum amyloid A (SAA) and C-reactive protein (CRP) in a study population that included 18 medication-free women with MDD who had been euthymic for at least 3 months and 18 healthy control women who were matched to the MDD patients in terms of body mass index. SAA levels were 86% higher and CRP levels were approximately 300% higher in the MDD women compared with the controls ($p < 0.005$ and $p < 0.01$, respectively). Using the accepted SAA cut-off values for intermediate and high risk of CAD (4 mg/L and 8 mg/L, respectively), significantly more MDD patients than controls had SAA levels that indicated intermediate risk and high risk (both $p < 0.01$). The findings were similar when accepted cut-off values for CRP for intermediate and high risk of CAD (1 mg/L and 3 mg/L, respectively) were analyzed.

An elevated inflammatory state has been proposed to be a common pathophysiological pathway of MDD and CAD. A previous study by this group of investigators found that levels of interleukin-6, a cytokine that stimulates CRP and SAA production, are increased in acutely depressed patients [1]. This study extends these findings, suggesting that a subacute inflammatory state may be a trait phenomenon in MDD. This study, which only investigated women, provides further evidence for an association between MDD and CAD, and suggests considering anti-inflammatory agents, such as aspirin, for MDD prophylaxis.

1. Alesci S, Martinez PE, Kelkar S et al. Major Depression is associated with significant diurnal elevations in plasma IL-6 levels, a shift of its circadian rhythm, and loss of physiologic complexity in its secretion: clinical implications. *J Clin Endocrinol Metab* 2005;90:2522–30.

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Erratum

In *Depression: Mind and Body* Vol 3 Iss 1, Dr Umair W Akhtar's name was incorrectly spelt throughout. We wish to apologise to Dr Akhtar for this mistake.

65th Annual Scientific Conference of the American Psychosomatic Society (APS)

Budapest, Hungary, March 7–10, 2007

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This year's American Psychosomatic Society (APS) Conference saw a great deal of new research on depression from around the world. A selection of research from the scientific symposia and poster sessions is presented with an emphasis on the association between depression and cardiac health.

Scientific symposia

Treatment of coronary artery disease in patients with depression

Several research groups presented new data on the relationship between depression and coronary artery disease (CAD). Wayne Katon (University of Washington School of Medicine, Seattle, WA, USA) and colleagues presented data from two studies – a comparison of post-surgical cognitive behavioral therapy (CBT), supportive stress management (SSM), and usual care in CAD patients with depression, and the Canadian CREATE (Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy) trial.

Kenneth Freedland (University of Washington School of Medicine) presented data from 123 patients with CAD and either major or minor depression. After receiving coronary artery bypass graft (CABG) surgery, patients were treated for depression with cognitive behavioral therapy (CBT), usual care, or supportive stress management (SSM). Assessment at 3 and 9 months after CABG surgery included the Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression (HAM-D). The results at 3 months post-surgery revealed that SSM caused a greater improvement in depression scores than usual care. In addition, the baseline diagnosis was found to affect the course of depression during the study period and to predict outcomes of depression; however, baseline diagnosis did not appear to influence the response to treatment. The data suggest that both CBT and SSM could be of benefit in the treatment of major and minor depression in patients after CABG surgery.

Francois Lesperance (Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada) offered a detailed

description of the CREATE trial, a 2x2 factorial randomized, placebo-controlled study of 284 outpatients with CAD and major depressive disorder (MDD). Subjects were randomized to receive 20–40 mg of citalopram or placebo and weekly sessions of interpersonal psychotherapy (IPT) or clinical management (CM) for 12 weeks. Eligible subjects had a history of bypass surgery, angioplasty, or myocardial infarction with currently stable CAD. All subjects had current MDD and scored ≥ 20 on the HAM-D at the start of the trial. The BDI was used as a measure of secondary outcome. At 6 weeks, the dosage of citalopram was increased from 20 mg to 40 mg, if tolerated, in subjects who scored > 8 on the HAM-D.

Brian Baker (University of Toronto, Toronto, ON, Canada) then presented the results of the CREATE trial. More than 83% of subjects completed all sessions of IPT or CM. By the end of the study, 70% were receiving 40 mg of citalopram or placebo. The data revealed that citalopram reduced more symptoms of depression than placebo (HAM-D difference of 3.3 points; $p=0.005$), a finding that remained significant at 6 weeks of treatment ($p=0.01$). In patients receiving citalopram, no additional benefit was seen with IPT (HAM-D difference of -2.3 points; $p=0.06$) suggesting CM is superior to IPT in reducing symptoms of depression. In a subgroup analysis, CM was found to reduce more symptoms of depression than IPT in patients with less functioning and social support. The data suggest that citalopram could be a first-line treatment for MDD in people with CAD and that additional IPT is not superior to CM in these patients.

Cortisol, heart rate variability, and depression in CAD

A symposium on the connection between depression and cardiovascular disease included a discussion on the evidence for an association between salivary cortisol levels and heart rate variability (HRV) and depression in patient with

suspected CAD. Additionally, evidence was presented on the relationship between depression and ambulatory HR, HRV, and salivary cortisol levels in a cohort of >1000 subjects. The symposium concluded with two presentations on possible genetic variations that may mediate the connection between cardiovascular disease and depression.

Mimi Bhattacharyya (University College London, London, UK) presented data from a study on 51 patients with suspected CAD examining the relationship between HRV and cortisol and measurements of mood and depressed affect. The BDI was used to assess depressed mood, and positive and negative affect was assessed by the Kaheman Day Reconstruction Method. The study revealed no association between BDI scores and HRV, although patients with BDI scores of >9 had flatter cortisol level slopes over the course of 1 day (7.39 nmol/L vs 11.9 nmol/L in subjects with BDI < 9). Additionally, a positive association was observed between positive affect and one measure of HRV (ratio of heart frequency to low frequency power). Therefore, the data suggest that positive and negative affect states, such as depressed mood, may be associated with specific biological functions in CAD patients.

Sophie Vreeburg (VU University Medical Center, Amsterdam, The Netherlands) presented data from the ongoing Netherlands Study of Depression and Anxiety, exploring the relationship between cortisol and depression and any modifying effect of antidepressant medication. Cortisol levels were assessed from saliva samples in 134 patients with MDD who were not on antidepressant medication, 100 MDD patients who were taking antidepressants, and 134 controls. There was no difference between any of the groups with respect to cortisol levels in the morning, evening, or before or after taking dexamethasone. This finding remained after health indicators and sociodemographic factors were taken into consideration. Therefore, the study suggests that depression might not lead to alterations in cortisol levels.

Carmilla Licht (VU University Medical Center) looked at measures of HRV and HR in subjects with or without MDD in The Netherlands Study of Depression and Anxiety. HR and a measure of HRV (root mean squared standard deviation [rMSSD]) were assessed for approximately three continuous hours in 357 control subjects, 375 subjects with current MDD, and 352 with non-current MDD history. Although HR did not differ significantly between groups, rMSSD was higher in the control group than in the MDD and lifetime non-current MDD group ($p=0.012$). Additionally, an inverse association was seen between rMSSD and severity of depression. This study offers data supporting the notion that MDD has an impact on HRV.

Poster sessions

The poster sessions presented a variety of research exploring the relationships between depression and cardiac health and risk factors.

Louis Zyl (Queen's University, Kingston, ON, Canada) et al. presented research on endothelium and platelet biomarker responses in depressed CAD patients treated with citalopram from the CREATE trial. The authors investigated 35 patients receiving 40 mg/day of citalopram and 23 on placebo. Subjects were permitted to use aspirin, anticoagulants, and clopidogrel as necessary. Endothelial and platelet biomarkers were assessed at baseline and 12 weeks after treatment. Patients on citalopram had increased total nitric oxide (NO) release compared with controls, suggesting that citalopram treatment in these patients may result in increased production of NO despite co-administration of anti-platelet medications.

Jürgen Barth (University of Berne, Berne, Switzerland) and colleagues presented data on the effects of depressive symptoms on the course of coronary heart disease (CHD). CHD subjects receiving inpatient cardiac rehabilitation who were involved in the PROTeCD (Psychotherapeutic Resource-Orientated Treatment for Cardiac Patients with Depression) intervention study were screened for depression. In all, 81 control and 40 depressed subjects were identified. The results showed that depressed patients had less improvement in mental quality of life 6 months after rehabilitation, although both groups had similar improvement in depression and other mental health symptoms. At 6 months after rehabilitation, non-depressed subjects had greater improvement in somatic health than depressed patients. However, by 12 months no differences were found between the groups with respect to any scale measured, suggesting that cardiac rehabilitation could result in decreased depressive symptoms.

Tina Harralson et al. (Drexel University School of Public Health, Philadelphia, PA, USA) presented data examining depression in cardiac patients in low-income urban demographics. Patients hospitalized for symptoms of acute myocardial infarction (AMI; $n=100$) were screened for depression by the Center for Epidemiological Studies Depression (CES-D) scale and assessed for cognitive and physical complaints of cardiac disease using the Health Complaints in Coronary Heart Disease (HCS) questionnaire. Higher CES-D scores were shown to correlate with poorer self-rated health, greater severity of AMI symptoms, current smoking, and younger age. Furthermore, symptoms of depression correlated with greater physical symptoms and increased HCS cognitive complaints. These findings suggest cardiac patients with higher depressive scores tend to report more cognitive and physical symptoms, poorer health, more

severe AMI symptoms, and tend to be younger than cardiac patients without depression.

Otto Smith et al. (Tilburg University, Tilburg, The Netherlands) presented research on the clinical significance of personality, prior depression, and cardiac history on depressive symptoms after MI. Patients who had recently had an MI (n=287) were screened for depression, placed into one of four categories (non-depressed, mildly, moderately, or severely depressed), and followed for up to 12 months. Multivariate analysis revealed cardiac history as the most significant risk factor for the development of depressive symptoms 12 months after MI. Additional determinants of depressive symptom trajectories included type-D personality and history of MDD.

Elizabeth Martens (Tilburg University) and coworkers presented research on the relationship between self-reported symptoms of anxiety and depression and adverse clinical events after an MI. Two months post-MI, 434 patients were screened for depressive and anxiety disorders. Follow-up at approximately 1.8 years revealed 26 non-fatal MIs and cardiac deaths. Analysis of the data from this group showed that the symptoms of anxiety and depression, but not the clinical diagnoses, significantly increased the risk of a cardiac event. Multivariate analysis revealed that only subjects with co-occurring depression and anxiety symptoms had a substantial increased risk of adverse events. Additionally, statin use and a cardiac history were independent predictors of death or MI. This study suggests that symptoms of depression and anxiety may be independent predictors of non-fatal MI or cardiac death, particularly when both disorders are present.

Paul Falger (University Hospital Maastricht, Maastricht, The Netherlands) presented data from a randomized controlled trial on anxiety, depression, and exhaustion after acute coronary syndromes (ACS). Of 213 subjects recruited into this study, 68% had experienced AMI and 32% had undergone CABG. Patients were screened for depression, exhaustion, and anxiety and followed-up at 1 year. Prior to the ACS, 20% of subjects were depressed and 44% were exhausted. Lifetime distress and baseline depression and exhaustion were predictive of depression and exhaustion at follow-up. Furthermore, baseline measurements on the Anger Expression Scale (AX) predicted depression, exhaustion, and AX measures at follow-up. In all, 22 subjects had new ACS during the follow-up period. In 68% of AMI patients, baseline Structured Clinical Interview

Depression module predicted ACS while other variables, such as cardiac history, did not. In addition, baseline depression was predictive of ACS at follow-up. This data suggest that 1-year cardiac morbidity, adverse mood, and depression may be partially predicted by baseline measures of negative affect, including exhaustion and depression, in ACS patients.

Anastasia Georgiades et al. (Duke University School of Medicine, Durham, NC, USA) offered information on the effects of depression on mortality in patients with CAD with or without diabetes mellitus (DM). In all, 907 patients with CAD hospitalized for coronary angiography were screened for depression using the BDI. Of these patients, 325 had DM. During the 4.5-year follow-up (mean 3 years), 135 deaths were documented and DM and depressive symptoms were independently associated with higher mortality rates ($p=0.004$ and 0.0002 , respectively). The highest mortality rate was seen in those subjects with DM and higher BDI scores ($p=0.09$). This study suggests that patients with CAD are at higher risk of death if they have both DM and symptoms of depression.

Elizabeth Martens (Tilburg University) et al. presented research examining whether anxiety and depression are predictive of HRV after MI. The study included 93 patients screened for current or lifetime depression and anxiety up to 2 months after having hospitalization for an AMI. Adequate 24-h ambulatory electrocardiography data were obtained in 82 patients at 4 months after discharge. After adjustment for socioeconomic factors, history of multi-vessel disease, and cardiac history, the data revealed that depressive disorder did not predict any HRV index that was assessed. However, anxiety disorder was predictive of several HRV indices. These findings suggest anxiety, but not depression, may have an impact on HRV in patients after an AMI.

René Krummenacher (University Hospital, Berne, Switzerland) and colleagues examined the relationship of depression with plasma D-dimer levels in patients with venous thromboembolism (VTE). VTE patients (n=65) had levels of plasma D-dimer determined and were assessed for depression. The data revealed that the interaction between social support and depression was a significant predictor of plasma D-dimer levels ($p=0.017$). In addition, the relationship between D-dimer levels and depression was significant in patients with low social support ($p=0.006$), but not in those with high social support ($p=0.029$). These findings suggest that psychosocial factors may increase the risk of recurrent of VTE.

DISCLOSURES

Dr Rasgon has served on advisory boards for Abbott, Eli Lilly, GlaxoSmithKline, UCLA General Clinical Research Center Medical Advisory Committee, Wyeth-Ayerst; consulted for Abbott and Wyeth-Ayerst; received funding or grants from Abbott, Forest, GlaxoSmithKline, National Institute of Aging, and National Institute of Mental Health; she has also participated in speakers bureaus for Abbott, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Pfizer, and Wyeth-Ayerst. Ms Zappert has no relevant financial relationships to disclose.

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Dr Nicholson has no relevant financial relationships to disclose.

ACCREDITATION

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Answers should be recorded in the spaces provided overleaf. One answer is correct for each question.

Biological and Psychosocial Correlates of Perimenopausal Depression: Implications for Treatment

Zappert LN and Rasgon NL.

Depression: Mind and Body 2007;3(2):50–6.

- The risk factors for menopausal mood disorders include:
 - Personal or family history of mood disorder or mental illness.
 - Ethnicity.
 - Psychosocial stressors.
 - A history of mood symptoms during other times of hormonal change.
 - All of the above.
- During the perimenopause, women can experience both somatic and psychological complaints, including everything but:
 - Hot flushes.
 - Breast tenderness.
 - Increased libido.
 - Fatigue.
 - Worsening of premenstrual syndrome.
- The “empty nest syndrome” refers to a psychosocial stressor which always increases the risk of perimenopausal depression.
 - True.
 - False.
- Pharmacological treatments for perimenopausal depression include:
 - Antidepressants.
 - Estrogen therapy (ET).
 - A combination of both.
 - All of the above.
 - None of the above.
- Both American College of Obstetricians and Gynecologists and the North American Menopause Society recommend that ET should be used for the longest duration consistent both with treatment goals and benefits/risks for individual women, taking into account quality of life issues.
 - True.
 - False.
- Estrogen may augment selective serotonin reuptake inhibitors during the perimenopausal transition.
 - True.
 - False.
- In the Kornstein clinical, findings included everything except:
 - Women were significantly more likely to show a positive response to sertraline than to imipramine.
 - Men responded more favorably to imipramine.
 - Postmenopausal women responded significantly better to imipramine than sertraline.
 - Perimenopausal women responded significantly better to sertraline than to imipramine.
- The NAMS stated that the Women’s Health Initiative data could not be extrapolated directly to patient groups other than:
 - Symptomatic perimenopausal women.
 - Symptomatic postmenopausal women.
 - Women experiencing early menopause (40–50 years old).
 - Women undergoing premature menopause (<40 years old).

Functional Neuroimaging in Treatment-Resistant Depression

Pardo JV, Sheikh SA, Schwindt GC et al.

Depression: Mind and Body 2007;3(2):57–70.

- Fluorodeoxyglucose positron-emission tomography (PET) is indicated for the diagnosis of treatment-resistant depression (TRD) when magnetic resonance imaging is negative.
 - True.
 - False.

- Identify key structures in affective illness:
 - Inferior colliculus and superior colliculus.
 - Inferior colliculus, superior colliculus, and subgenual cingulate.
 - Superior colliculus and subgenual cingulate.
 - Subgenual cingulate, hypothalamus, and amygdala.
 - Amygdala and inferior colliculus.
- Identify treatments for TRD that are approved by the Food and Drug Administration in the US:
 - Aripiprazole and deep brain stimulation.
 - Fluoxetine and vagus nerve stimulation.
 - Aripiprazole and repetitive transcranial magnetic stimulation (rTMS).
 - Aripiprazole and deep brain stimulation.
 - Aripiprazole and vagus nerve stimulation.
- PET scans in neuropsychiatry are never covered by Medicare and other insurance carriers when used in the differential diagnosis between Alzheimer’s disease and frontotemporal dementia.
 - True.
 - False.
- Which of the following is often seen upon successful treatment of depression?
 - Decreased metabolism in the dorsolateral prefrontal cortex.
 - Decreased metabolism in the ventromedial prefrontal cortex (VMPFC).
 - Increased metabolism in the sensorimotor cortex.
 - Increased activity in the amygdala.
 - Deactivation of the red nucleus.
- Which of the following is true?
 - The amygdala deactivates upon exposure to aversive smells and tastes.
 - rTMS appears effective through deactivation of the nucleus of the solitary tract.
 - Most TRD patients get well in 2 years with treatment as usual (current standard of care).
 - “Vascular depression” is a major cause of TRD.
 - TRD patients with personality disorders portend a worse course.
- Mrs Smith reports that she has been diagnosed with TRD. She returns for a follow-up appointment. She is at the maximum recommended dose of her antidepressant, but she is not improving. What would be the reasonable next step(s)?
 - Ask about her compliance with taking her medications.
 - Ask whether she smokes cigarettes.
 - Check her blood pressure and pulse.
 - Check what other medications she is taking.
 - All of the above.
- The relationship between activity in the amygdala and the VMPFC follows:
 - Positive correlation.
 - Negative correlation.
 - No correlation.
 - Depends on dopamine from the ventral tegmental area.
 - The amygdala is not connected to the VMPFC.
- Pulse frequencies used to treat patients with TMS include:
 - Only frequencies <1 Hz.
 - 1 Hz and 10 Hz.
 - 10 Hz and 100 Hz.
 - 100 Hz and 1 kHz.
 - Only frequencies >1 kHz.
- Which of the following does not apply to the VMPFC?
 - Role in decision making.
 - Self-reference.
 - Connection to sensory cortex.
 - Irrational economic choices.
 - Galvanic skin response.

Psychiatric Disorders and the Risk of Coronary Heart Disease

Nicholson A.

Depression: Mind and Body 2007;3(2):71–5.

- Which of the following is false regarding the association between coronary heart disease (CHD) and depression?
 - Meta-analyses have estimated that depression may be responsible for a 20–25% increased risk of CHD in etiological studies.
 - Mild symptoms of depression have been correlated with an increased risk of CHD in both etiological and prognostic studies.
 - When assessing the independent risk of depression on CHD, many etiological studies have incompletely controlled for known risk factors.
 - Study results demonstrating an association of a recent increase in patients’ depressive scores with future development of CHD suggest reverse causality.
 - Some investigations have found an increased risk of CHD following decades of depressive disorder.
- Antidepressant treatment in patients who have experienced myocardial infarction (MI) has been investigated in randomized trials, demonstrating that it:
 - Improves CHD prognosis but not depression.
 - Improves both CHD prognosis and depression.
 - Improves depression but not CHD prognosis.
 - Has no effect on either CHD prognosis or depression.
 - Is not to be recommended due to safety concerns in this patient group.
- Psychological therapy in post-MI patients has been shown to be more efficient in reducing the risk of recurrent MI or death than pharmacological treatment.
 - True.
 - False.
- Which of the following statements about the effect of depressive symptoms on CHD risk is true?
 - The effect of depressive symptoms on CHD risk has been clearly shown to be independent from other negative emotions and personality traits.
 - The effect of depressive symptoms on CHD risk has been clearly shown to be dependent on other negative emotions and personality traits.
 - The extent to which the effect of depressive symptoms on CHD risk is independent from other negative emotions and personality traits has been poorly investigated.
- Although there are no recent confirmatory reports, the strongest evidence in the anxiety literature supports an etiological link between future sudden cardiac death and:
 - Obsessive neurosis.
 - Obsessive neurosis and phobic anxiety.
 - Obsessive neurosis and somatic complaints.
 - Phobic anxiety.
 - Phobic anxiety and somatic complaints.
- Standardized mortality ratios in schizophrenia patients:
 - Are larger for cardiovascular disease than for cerebrovascular, respiratory, and digestive diseases.
 - Are smaller for cardiovascular disease than for cerebrovascular, respiratory, and digestive diseases.
 - Are the same for cardiovascular disease and for cerebrovascular, respiratory, and digestive diseases.
 - Have not been calculated for different diseases.

Complete the post-test answer sheet, evaluation form, and registration form, and return to:
 Attn: Distance Education
 UKCPMCE [MEN07334]
 One Quality Street, 6th Floor
 Lexington, KY 40507, USA
 Fax: (859) 323-2920

Alternatively the form can be downloaded from www.depressionmindbody.com by following the links to CME. Registration is required but is free to physicians and healthcare professionals.

EXAMINATION ANSWERS

Record your answers here by filling in the blank with the correct letter for the corresponding question:

Biological and Psychosocial Correlates of Perimenopausal Depression: Implications for Treatment. Zappert LN and Rasgon NL. *Depression: Mind and Body* 2007;3(2):50–6.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____

Functional Neuroimaging in Treatment-Resistant Depression. Pardo JV, Sheikh SA, Schwindt GC et al. *Depression: Mind and Body* 2007;3(2):57–70.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____

Psychiatric Disorders and the Risk of Coronary Heart Disease. Nicholson A. *Depression: Mind and Body* 2007;3(2):71–5.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____

Participants will receive a confidential report of their results along with the correct answers to each question. A certificate of credit will be sent to those who successfully complete the examination.

EVALUATION FORM

Strongly agree ←————→ Strongly disagree

1. The activity provided new information I had not yet acquired.	1	2	3	4	5
2. The activity helped increase my knowledge and skills.	1	2	3	4	5
3. The activity content was educational and understandable.	1	2	3	4	5
4. The activity content met its objectives.	1	2	3	4	5
5. The amount of information presented was adequate for my needs.	1	2	3	4	5
6. I felt I absorbed a reasonable amount of the presented materials.	1	2	3	4	5
7. The technical quality of the activity was acceptable.	1	2	3	4	5
8. I would recommend this program to my peers.	1	2	3	4	5
9. Funding for this activity may have come from commercial sponsors. Do you think you were adequately informed of commercial sponsorship or faculty conflict of interest?				Yes	No
10. Do you think the overall activity was biased toward certain commercial products or services?				Yes	No

REGISTRATION FORM

Name:

Affiliation:

Office Address:

.....

City: State: Zip Code:

Office Phone: Home Phone:

Email:

Physician License No./State:

By signing this certificate, I attest that I have attended the above named continuing medical education program.

Signature: Credit Hours:

NEEDS ASSESSMENT

Depression: Mind and Body, a CME-accredited educational program, systematically identifies, evaluates, and places into clinical context the most important recent studies into the science and medicine of depression. It provides rapid access for busy specialists to a critical and clinically relevant review of the developments that will have most impact on their day-to-day practice and is designed to provide management options for clinicians to allow them to better diagnose and treat patients with depression.

Each issue of *Depression: Mind and Body* will present carefully constructed leading (review) articles, written by practicing psychologists, and intended to equip readers with practical knowledge of the area under discussion. These articles are commissioned to support particular educational themes identified by the Editor-in-Chief and readers. This issue of *Depression: Mind and Body* presents three such leading articles.

LEARNING OBJECTIVES

Biological and Psychosocial Correlates of Perimenopausal Depression: Implications for Treatment
 Zappert LN and Rasgon NL.

Depression: Mind and Body 2007;3(2):50–6.

Goal: To review the data on psychosocial and biological correlates of mood disorders during perimenopause, and the implications for treatment.

Objectives: After reading this article the reader should be able to discuss:

- The psychosocial and biological factors that predispose women to mood disorders during perimenopause
- Different pharmacological treatments for perimenopausal depression

Functional Neuroimaging in Treatment-Resistant Depression

Pardo JV, Sheikh SA, Schwindt GC et al.

Depression: Mind and Body 2007;3(2):57–70.

Goal: To review the role of functional brain imaging in the management of treatment-resistant depression (TRD), and to discuss two new electromagnetic treatments – repetitive transcranial stimulation (rTMS) and vagus nerve stimulation (VNS).

Objectives: After reading this article the reader should be able to:

- Discuss the role of functional neuroimaging in TRD
- Discuss the different neural structures that are relevant to TRD
- Describe rTMS and VNS, and discuss trial outcomes and future potential for their use in the treatment of TRD

Psychiatric Disorders and the Risk of Coronary Heart Disease

Nicholson A.

Depression: Mind and Body 2007;3(2):71–5.

Goal: To review the literature published to date on the hypotheses that depression, anxiety, and schizophrenia are independent risk factors for coronary heart disease (CHD)

Objectives: After reading this article the reader should be able to discuss:

- The data indicating a causal association between depression and CHD, and those that suggest reverse causality
- The study data on anxiety as a risk factor for CHD
- The study data on schizophrenia as a risk factor for CHD

DEPRESSION: MIND AND BODY

Reader Survey – Let Us Know What You Think!

Please take a few moments to complete this survey. We would value your opinion.

Please photocopy this page, complete the survey below, and fax it back to Remedica on **+44 (0)20 7759 2951**. Or you can visit the *DEPRESSION: MIND AND BODY* website and complete the survey online (registration online is FREE):

www.depressionmindbody.com

1. We are aiming to provide practical information for practicing psychiatrists and healthcare professionals. How would you rate the information presented in this issue?

Strongly agree ← → Strongly disagree

- | | | | | | |
|--|---|---|---|---|---|
| a) The technical quality of information included in <i>DEPRESSION: MIND AND BODY</i> was acceptable: | 1 | 2 | 3 | 4 | 5 |
| b) The information was relevant to my practice: | 1 | 2 | 3 | 4 | 5 |
| c) The information was presented clearly: | 1 | 2 | 3 | 4 | 5 |
| d) The leading articles provide new information regarding the understanding and treatment of depression: | 1 | 2 | 3 | 4 | 5 |
| e) The clinical review section was helpful and I would like to see analyses in future issues: | 1 | 2 | 3 | 4 | 5 |

2. Did you learn anything through the CME activity *DEPRESSION: MIND AND BODY* that will change the way you practice medicine?

Yes No

If so, what?.....

3. Is there anything you learned from the CME activity *DEPRESSION: MIND AND BODY* that prompts you to seek further information that may influence the way you practice medicine in the future?

Yes No

If so, what?.....

4. Would you like to recommend *DEPRESSION: MIND AND BODY* to a colleague?

Yes No

My colleague's email is:

5. What specific topics do you think should be covered in future issues?

.....

Name Job title

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