Hormone treatment of depression

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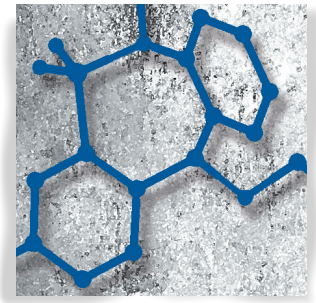

There is a well-established relationship between alterations of various hormonal systems and psychiatric disorders, both in endocrine and psychiatric patients. This has led to clinical and research studies examining the efficacy of the different hormones for treatment of depression. These data will be reviewed with particular regard to the thyroid, gonadal, pineal, and adrenal cortex hormones. The data generally provide limited, but varying evidence for the antidepressant efficacy of these hormones.

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Clinical endocrine disorders have long been recognized to have psychiatric symptoms as a prominent feature of their clinical presentation. Both hyper- and hypofunction of the various endocrine glands have led to a wide range of psychiatric symptoms and syndromes, most commonly depression. Moreover, treatment of the endocrine condition frequently results in resolution of the psychiatric sequelae. These observations in endocrine patients led to a comprehensive search for a hormonal etiology for many psychiatric disorders, particularly major depression and bipolar disorder. While this research effort was largely unsuccessful, with the possible exception of perturbations of the adrenal axis in major depression (see below), it did lead to substantial enquiry into whether various hormones may have clinically useful antidepressant efficacy in primary major depression and, to a lesser extent, bipolar disorder. While there are a number of case reports and small case series documenting the antidepressant effects of a large number of hormones of various endocrine systems, there is a limited database on just a few endocrine systems, which include large open trials or randomized controlled trials. This review will focus on these hormones which include:

- Hormones of the thyroid axis
- Gonadal steroids, which include testosterone in men and gonadal steroids in women
- Melatonin
- Adrenal cortex hormones.

Thyroid hormones

Disorders of the thyroid axis have been closely linked to psychiatric disorders.[1] While hyperthyroidism may present with a heterogenous range of psychiatric symptoms and syndromes, clinical hypothyroidism is invariably

associated with depressive symptoms.[1] Although extensive research has shown that the vast majority of patients who present with major depression are euthyroid,[2] the close association between depression and hypothyroidism led to a large database of studies in which various hormones of the thyroid axis have been used to treat depression as monotherapy or, more commonly, as adjunct to standard antidepressants. Each of the hormones of the thyroid axis will be reviewed.

Thyrotropin-releasing hormone

Thyrotropin-releasing hormone (TRH) is a hypothalamic peptide that regulates thyroid hormone secretion by the thyroid gland through its effect on pituitary thyroid-stimulating hormone (TSH) release. TRH is also a peptide that occurs in brain, and has behavioral effects such as reversal of drug-induced sedation or anesthesia and stimulation of locomotor activity independent of its effect on the thyroid.[3] Due to its stimulation of the thyroid axis, as well as its independent effects on brain function, it has been tested as an antidepressant. Most studies have involved monotherapy, but there have also been studies of the use of TRH together with electroconvulsive therapy (ECT). These studies are reviewed in *Table I*.
TRH has been administered to patients intravenously[4-12] and by oral routes[13-15] for depression. TRH has been administered intravenously either as a single dose[4-6] or as several doses over 3 to 4 days,[7-12] and transient antidepressant effects have been demonstrated.[4-15] However, at least half of these studies have reported no or very minimal therapeutic response to either intravenous or oral TRH administered as monotherapy with duration of treatment ranging from a single dose up to 30 days (see *Table I*). Although a positive effect on depressed mood cannot be definitively excluded, it is very difficult to determine whether TRH has a significant therapeutic role in the treatment of depression, because of its very short duration of action and its stimulant effects independent of the thyroid axis. Moreover, the transient effects noted may have little to do with the thyroid axis and may be a nonspecific activating effect of the neuropeptide.[3] A later study used a randomized, double-blind, placebo-controlled, crossover design in which 500 g of TRH was administered to eight depressed patients who also received ECT for their depression. TRH administered intravenously before the ECT led to greater arousal and improved cognitive function when compared with placebo. TRH did not have any substantial effect on any seizure variables. This is a small study that may suggest an alternative indication for TSH in the treatment of depressed patients.[16]

Thyrotropin

Thyrotropin (TSH) is a pituitary hormone which stimulates the thyroid gland, and thus would be expected to achieve an effect similar to the administration of peripheral thyroid hormones for the treatment of depression.[17] One study to date has examined the antidepressant effect of TSH. Prange and collaborators[18] administered ten IU of TSH intravenously to 20 depressed women 1 day before beginning an antidepressant trial with the tricyclic imipramine. The TSH-treated patients had a rapid antidepressant response when compared with a placebo control group. There are no replication studies, and clearly the intravenous administration required would limit the clinical utility of this hormone.

Tri-iodothyronine

The thyroid gland secretes two major hormones, levothyroxine (T4) and tri-iodothyronine (T3).[17] T4 is the major secretory product of the thyroid, and most T4 undergoes peripheral conversion to T3 in order to exert its physiological action.[17] T3 is the most broadly used thyroid hormone for treatment of depression, in contrast to in endocrine patients where T4 is routinely used for thyroid replacement therapy.[17] In early studies, T3 was used as monotherapy for the treatment of depressed patients.[19,20] The data from these studies are largely inconclusive, as they involved small patient samples, inadequate clinical trial designs by current methodological standards, and the use of heterogeneous patient

Number of studies	Total N	Route of administration	Duration	Positive studies (TRH>placebo or =antidepressant)
3	36	IV	Single dose	1
6	86	IV	3–4 days	1
3	52	Oral	7–30 days	1

Table I. Antidepressant effect of thyrotropin-releasing hormone (TRH).

groups who, by today's diagnostic criteria, would not necessarily have major depression. There have been no well-designed studies of T3 monotherapy to date, and, therefore, its use as a single treatment for depression has not gained any clinical use.

T3 has been used in three other ways in the treatment of depression:

- In the initial few weeks of an antidepressant trial to reduce the delay in antidepressant effect—acceleration studies
- To improve treatment response in those who do not respond adequately to an antidepressant trial—augmentation studies
- To enhance antidepressant response by being used throughout the antidepressant trial—enhancement studies.

Acceleration studies

These studies are reviewed in *Table II*. In the first of these studies in 1969, Prange and collaborators[21] used T3 to accelerate the response to tricyclic antidepressants. In several studies,[21,22,24] they demonstrated that if T3 was administered at the outset of a tricyclic antidepressant trial, there was a shorter lag in onset of therapeutic effect as compared with placebo controls. This acceleration effect was noted particularly in women as compared with men.[21-26] In the next few years, several studies were performed, some of which replicated these findings, although some had negative results. These studies are reviewed in *Table II*. All of these studies had major methodological flaws, including small numbers of patients, poorly defined patient groups, and relatively brief duration of treatment, as well as the use of tricyclic antidepressants rather than selective serotonin reuptake inhibitors (SSRIs) at suboptimal doses by current standards.

Augmentation studies

T3 has most commonly been used to augment response to antidepressants in those who failed to respond to an antidepressant trial. These studies are reviewed in *Table III*. These studies, whether open-label or controlled, generally

Study	N	Dose T3 (μg/day)	Antidepressant	Day T3 added	Duration	Acceleration
Prange et al, 1969[21]	20	25	Imipramine	5	28	+
Wilson et al, 1970[22]	20	25	Imipramine	5	28	+
Coppen et al, 1972[23]	15	25	Imipramine	1	28	+
Feighner et al, 1972[24]	21	25	Imipramine	1	22	_
Wheatley, 1972[25]	30	20	Amitryptiline	1	21	+
Wilson et al, 1974[26]	19	Up to 62.5	Imipramine	3	28	+

Table II. T3 acceleration of antidepressant response.

Study	N	T3 dose (μg/day)	Design	Result
Earle, 1970[27]	25	25	Open	14 of 25 responded
Ogura et al, 1974[28]	44	20–30	Open	29 of 44 responded
Banki, 1975[29]	52	20–40	Open	39 of 52 responded
Banki, 1977[30]	33	20	Partially controlled	23 of 33 responded
Tsutsui et al, 1979[31]	11	5–25	Open	10 of 11 responded
Goodwin et al, 1982[32]	12	25–50	Double-blind	8 of 12 responded
Schwarcz et al, 1984[33]	8	25–50	Open	4 of 8 responded
Gitlin et al, 1987[34]	16	25	Double-blind, crossover	T3 = placebo
Thase et al, 1989[35]	20	25	Open	5 of 20 responded
Joffe and Singer, 1990[36]	38	37.5	Double-blind	9 of 17 responded
Joffe et al, 1993[37]	51	37.5	Double-blind, placebo-controlled	10 of 17 responded to T3, T3 > placebo, T3 = (lithium?)
Birkenhager et al, 1997[38]	14	37.5	Open	No response—all inpatients
Agid & Lerer, 2003[39]	74	25-50	Open, added to SSRI	44/74 responded at 4 weeks

Table III. T3 augmentation of antidepressants.

show that up to half of patients who do not respond to an antidepressant trial will respond within 2 to 3 weeks after the addition of 25 to 50 g of T3. The notable exception is the study by Gitlin et al[34] who failed to find a significant difference between T3 and placebo in the potentiation of imipramine in 16 patients with major depression. This study, however, involved a 2-week, double-blind, crossover design, which can be problematic in evaluating antidepressant treatment response. Another study compared T3 augmentation to lithium augmentation in tricyclic antidepressant nonresponders.[37] Both augmentation strategies were found to be comparable in a 2-week placebo-controlled trial. This was the first study to directly compare lithium and T3 in tricyclic augmentation, but later studies did examine T3 versus lithium with SSRI nonresponders[41,42] (see *Table III*). In view of the limitations of the individual studies involving tricyclics, a meta-analysis of these studies concluded that T3 may increase response rates and decrease severity of depression scores in patients refractory to tricyclic antidepressant treatment.[43] Patients with T3 augmentation were approximately twice as likely to respond as were controls. Recently, there has been emerging data on the use of T3 to augment SSRIs,[39-42] the most commonly used antidepressants. The findings with the SSRIs are generally consistent with those for the tricyclics. Both open and controlled studies are generally positive, and indicate that T3 may be an effective augmentation agent for SSRI nonresponders. Recent data from the STAR*D trial[42] showed that T3 augmentation had comparable response and remission rates to other augmentation options such as lithium, and a more favorable adverse event dropout rate, despite the fact that response and particularly remission rates were low in all treatment groups.

Enhancement studies

Cooper-Kazaz and collaborators[44] termed this group enhancement studies, when T3 is added to an SSRI at the outset of the antidepressant trial and is administered throughout the acute treatment period. These studies are summarized in *Table IV*. These studies provide virtually no support for an acceleration effect of T3 when administered with SSRIs with only the Posternak et al[47] study showing a trend toward acceleration. As far as enhancement of SSRI response is concerned, the data are conflicting, with one positive,[46] one negative,[45] and one trending study.[47] The enhancement studies should probably be considered separately from the augmentation studies. In the latter, patients have responded inadequately to an antidepressant and show some benefit with T3 addition whereas with enhancement studies, subjects include both potential responders and nonresponders to antidepressants and the aim is to accelerate and enhance rates of antidepressant response rather than to convert nonresponders to antidepressant responders.

Thyroxine

This thyroid hormone has been used in two ways in the treatment of mood disorders. First, it has been used as an augmentation agent for the treatment of antidepressant nonresponders, and, second, as a mood stabilizer for rapid-cycling bipolar disorder. The latter will not be discussed. T4 has received less attention as an augmentation agent, as most of the initial studies were carried out using T3. However, there is a limited database on the use of T4 augmentation, and these studies are summarized in *Table V*.

Study	N	T3 dose (μg/day)	Design	Result
Appelhof et al, 2004[45]	113	25 vs 50	RCT, placebo-controlled	T3 25 μg=T3 50 μg=Placebo
Cooper Kazaz et al, 2007[46]	124	50	RCT, placebo-controlled	Response T3=70%, Placebo=50%
Posternak et al, 2007[47]	50	50	RCT, placebo-controlled	Response T3=51%, Placebo=33%

Table IV. T3 Enhancement of antidepressants.

Study	N	Patients	T4 Dose (μg/day)	Design	Response
Joffe and Singer, 1990[36]	38	Unipolar major depression	150	Double-blind vs T3	4 of 21 responded to T4, T4 < T3
Bauer et al, 1998[48]	17	Unipolar (or) bipolar depression	300–500	Open	10 of 17 showed full or partial response
Spoov and Lahdelma, 1998[49]	22	Major depression	200	Crossover vs lithium	T4 > lithium
Rudas et al, 1999[50]	9	Chronic depression and dysthymia	150–300	Open	6 of 9 full or partial response
Lojko and Rybakowski, 2007[51]	17	Unipolar and bipolar depression	100	Open, on SSRI	11 remission and 16 response

Table V. Antidepressant augmentation with T4. T3, tri-iodothyronine; T4, thyroxine; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor

These studies generally involve open designs using various diagnoses, including both unipolar and bipolar subjects in one study[48] and chronic depression or dysthymic patients in another study.[50] All involve small sample designs. Nonetheless, in each of these studies, T4 showed augmentation effects in antidepressant nonresponders.

The efficacy of T4 and its comparable efficacy to T3 remain unresolved issues. A large-scale, well-designed, placebo-controlled study directly comparing the efficacy T3 and T4 in SSRI nonresponders with major depression would address this important issue.

In conclusion, the database on thyroid hormone treatment provides mixed findings in studies, often with methodological limitations and inconclusive data. The strongest evidence is for an antidepressant augmentation effect of T3 in antidepressant nonresponders, but the use of T3 in other ways to accelerate and enhance antidepressant treatment, as well as the clinical utility of other hormones of the thyroid axis, require further study. In addition, issues such as tolerability, long-term safety, and duration, as well as dose of treatment need to be addressed. The doses employed in all these studies are less than the amount of endogenous T3 daily production so that there is little risk of induction of clinical hyperthyroidism.

Another important issue for future study is whether particular subtypes of depression respond preferentially to thyroid hormone or in fact any hormonal treatment. As greater knowledge is obtained about genetic and biological variability of major depression as well as the regulation of thyroid hormones in the body in general and the brain in particular, we may be able to identify preferential responders to thyroid hormone and, analogously, to other hormone strategies.

Gonadal hormones

Testosterone

There are several lines of evidence, both clinical and research, that support the idea that testosterone and similar androgens may be useful in the treatment of depressed men. First, hypogonadism, usually pharmacologically induced, is associated with depressive symptoms and low libido,[52,53] and androgen replacement is often associated with improvement in mood, energy, and libido[54-56] in some but not all studies, although this literature is also inconsistent.[57,58] Second, some but not all studies suggest an association between low testosterone levels and depressive symptoms.[59,60] Last, supraphysiological doses of androgens may be associated with manic or hypomanic symptoms in some individuals,[61] and hypogonadism during withdrawal from long-term anabolic steroid use may be associated with depression.[61] These observations have led to numerous studies examining the effect of androgens in the treatment of depression. Earlier, open-label studies suggested that androgens may be effective for treating depression, especially in men who are hypogonadal.[62-65] Recently, there have been several studies using controlled designs where testosterone was used to treat depression in men who were hypogonadal or had low normal levels of testosterone. Testosterone was administered as monotherapy or else as an adjunct to conventional antidepressants. These studies are summarized in *Table VI*. The findings from these studies are inconsistent, producing positive, negative, and inconclusive results.[66-74] Some of these differences may be due to methodological issues as noted in *Table VI*, although the weight of evidence would suggest that testosterone may have some antidepressant benefits in hypogonadal men. Further study is required before definitely concluding that testosterone is a clinically useful treatment for depression. The limited database and inconclusive findings in some studies have to be weighed against the known side effects of testosterone administration such as hypertension, gynecomastia, and polycythemia as well as the fact that treatment emergent paranoid symptoms have been infrequently reported especially in earlier studies.[62-65] The potential increased risk for prostate cancer with long-term testosterone treatment remains an unresolved issue.[75,76]

Ovarian hormones

The neuromodulatory effects of the ovarian steroids are well established.[77-79] Substantial changes in estrogen levels can have effects on brain function and, therefore, on mood and cognition.[79] The cyclic changes in gonadal steroids that occur with the menstrual cycle is one example of a period of vulnerability for psychiatric symptoms as a consequence of these fluctuations.[80] It follows that depressive symptoms and depressive disorders occur at important stages of a women's life at times when the reproductive cycle is associated with changes in ovarian hormone levels, thus providing a rationale for the use of

hormonal treatment for depression. In addition to premenstrual depression, there is also greater vulnerability to depression in the postpartum and peri/postmenopausal period. Each will be briefly reviewed.

Premenstrual depressive symptoms

Most women will report premenstrual symptoms at some point in their lives.[81] About one fifth of women will report more severe symptoms, including depression, and about 3% to 8% will meet criteria for the diagnosis of Premenstrual Dysphoric Disorder (PMDD).[82] A wide variety of treatment options have been utilized for patients where symptoms interfere with daily function or quality of life. These are not limited to pharmacological options, and hormonal treatment represents a very small component of the overall approach to this condition.[83] Hormonal therapy of premenstrual symptoms involves suppression of ovulation by using oral contraceptives,[83] gonadotrophin-releasing hormone agonists (GnRH agonists), and danazol in order to break the cyclic recurrence of mood symptoms. These are usually employed when standard antidepressant treatments are ineffective.[83] GnRH agonists have been shown to be variably effective in reducing psychiatric morbidity in several placebo-controlled trials.[84-86] For the most part these studies have varying methodological limitations.[84-86] In addition, side-effect burden is a problem with the GnRH agonists, particularly those relating to hypoestrogenism which are only partially ameliorated by add-back estrogen and progestogen therapy.[84-86] The reduction in bone mass with these compounds limits duration of treatment to no more than 6 to 9 months.[83]

Various formulations of oral contraceptives have been used to treat premenstrual symptoms. In general, these have had mixed results in improving these symptoms in open and controlled trials.[87-90] The general consensus is that oral contraceptives of any formulation are more likely to be beneficial in treating physical symptoms of premenstrual syndrome and have less demonstrated efficacy with depressive and related psychiatric symptoms.[87-90]

Danazol is an androgen-like agent which inhibits gonadotropin release and, thereby, ovulation, and has been shown in several controlled trials to reduce symptoms of premenstrual syndrome.[91-93] However, its androgenic side effects, particularly masculinization, as well as

Study	Subjects	Design	Testosterone	Antidepressant	Result
Seidman and Rabkin, 1998[66]	5 men Low testosterone levels	Open 8 weeks	400 mg im biweekly	Yes	Marked improvement
Seidman et al, 2001[67]	32 men Hypogonadal	RCT 6 weeks	200 mg im q-weekly	Yes	Testosterone=Placebo
Perry et al, 2002[68]	16 Older males	Open 6 weeks	200 mg vs 100 mg qweekly	No	No dose effect Improvement late onset > early onset depression
Pope et al, 2003[69]	22 Low testosterone levels	RCT 8 weeks	Gel 1% 10 g/day	Yes	Testosterone>placebo
Orengo et al, 2005[70]	61 Hypogonadal men >50 y	RCT 12-week crossover	Gel 1% 5 g/day	Yes	Testosterone=placebo
Seidman et al, 2005[71]	26 Healthy adult men	RCT 6 weeks	im	Yes	Testosterone=placebo
Seidman et al, 2009[72]	23 Men, low testosterone Dysthymic	RCT 6 weeks	im q10 days	No	Testosterone>placebo
Shores et al, 2009[73]	33 Men >50 y hypogonadal Dysthymic	RCT 12 weeks	Gel 1% 7.5 g/day	Yes	Testosterone>placebo
Pope et al, 2010[74]	100 Adult men Low testosterone levels	RCT 6 weeks	Gel 1%	Yes	Testosterone=placebo

Table VI. Testosterone treatment of depression.

adverse effects on liver function and lipid parameters, seriously limits its clinical utility.[91-93]

Postpartum depression

The postpartum period is characterized by a sharp reduction in circulating estrogen levels, which provides a rationale for the use of estradiol to treat this disorder. A recent open and controlled trial provided support for the efficacy of estradiol therapy.[94,95] In the open trial, 21 of 23 postpartum severely depressed women responded to sublingual 17b-estradiol (4.8 mg/d) for 8 weeks.[94] In the controlled trial, where subjects received high dose transdermal 17b-estradiol (200 g/d) for 6 months in addition to antidepressants, the active treatment had a significantly greater antidepressant effect compared with placebo over the course of treatment.[95]

Perimenopausal/postmenopausal period

During this life phase, there is an increasingly erratic cyclic variation in estrogen and progestogen followed by increasing periods of estrogen withdrawal. During this phase there is a significant increase in the risk for major depression, especially in those women who have a past history of depressive episodes.[96] As with any other stage of life, treatment of depressive disorder in the peri- and postmenopausal period usually involves antidepressant treatment. However, given that this phase of life is associated with progressive ovarian failure and hypoestrogenism, the role of estrogen replacement therapy in the treatment of depression has been a focus of research.[97-101] In some but not all open-label and placebo-controlled studies,[97-101] estrogen has been shown to reduce both physical and depressive symptoms. In particular, two of three recent controlled trials[99-101] documented the efficacy of estrogen replacement therapy in reducing depression in postmenopausal women. Estrogen replacement therapy may also enhance antidepressant response in such women.

The potential clinical efficacy of estrogen in postpartum and postmenopausal depression, or in any other psychiatric indications associated with altered gonadal function, has to take side effects into consideration.[83-101] Common side effects include gastrointestinal dysfunction, headaches, and exacerbation of migraine as well as breast tenderness, vaginal bleeding, and infection. Hypertension and venous thrombosis are also concerns, although this risk is potentially reduced by use of transdermal rather than oral estrogen preparations.[83-101] The relationship between estrogen therapy and risk of breast and uterine cancer is beyond the scope of this review, but remains an issue to consider in instituting estrogen treatment for these various depressive syndromes.

Pineal gland

Melatonin is the major secretory hormone of the pineal gland. One of the main physiological effects of melatonin is the regulation of circadian rhythms.[102] Given the prominence of sleep disturbance and the demonstrated alteration of various circadian parameters in major depression,[103] several studies have attempted to determine whether a specific abnormality of melatonin secretion could be demonstrated in major depression and, further, whether it could be of potential etiological significance.[104] Findings from these studies have been inconsistent with many showing decreased amplitude of the nocturnal surge of melatonin while others showed increased or no change in nocturnal melatonin secretion.[104] The-well described sedative effect of this hormone and its effect on circadian function has led to its widespread use in insomnia, jet lag, and difficulties associated with shift work.[105]

The use of melatonin as an antidepressant has been examined in both seasonal and nonseasonal depression. In seasonal depression, although a normalizing phase advance has been consistently demonstrated, the antidepressant action of melatonin has been inconsistent.[106,107] In seasonal depression, the first report actually demonstrated worsening of depressive symptoms in a study of 6 depressed subjects given intravenous melatonin at varying but usually high doses.[108] This study abated enthusiasm for examining the antidepressant effects of melatonin for some time, but a subsequent group of better designed studies have emerged. These are summarized in *Table VII*. These studies continue to document the hypnotic effects of melatonin, but produce inconsistent findings as far as antidepressant effects are concerned. The studies do however, involve small samples and limited follow-up, making it difficult to reach a definitive conclusion about the clinical efficacy of melatonin as an antidepressant. Further study is necessary to definitively assess the extent of the antidepressant effect of melatonin and its potential role relative to standard antidepressant treatments.

In addition to the use of the actual hormone melatonin, agomelatine, acting at both the melatonin-1 and melatonin-2 receptor, is the first melatonergic agonist to have been developed as an antidepressant. This compound resynchronizes circadian rhythms which have been altered in animal models, and also normalizes circadian rhythms in depressed subjects.[115] It has been shown to have acute antidepressant effects superior to placebo and comparable to, or even more favorable than, standard antidepressants such as sertraline, fluoxetine, and venlafaxine in several controlled trials.[115-118] It is also generally well tolerated. Agomelatine may not only represent a new class of antidepressant with a different tolerability profile, but it may also provide indirect evidence that melatonin may be involved in the cascade of biological events associated with the etiology and treatment response of major depression.

Adrenal axis hormones

There is a well-described relationship between hypercortisolism and depressive symptoms in both psychiatric and endocrine patients.[119] Approximately half of all severely depressed subjects have elevated levels of cortisol,[119] and depression is a frequent complication of both Cushing's syndrome as well as with longer-term treatment with exogenous corticosteroids.[119] These observations have led to the notion that interference with cortisol secretion may produce antidepressant effects. This approach to hormonal treatment of depression involving the adrenal axis means reducing the levels and effects of adrenal hormones rather than enhancing hormone levels by exogenous administration as has been discussed with the other hormonal systems.

Major depression may be associated with a defect at or above the level of the hypothalamus resulting in the hypersecretion of corticotrophin-releasing hormone (CRH) and, therefore, leading to hypercortisolism.[119] Various strategies to reduce adrenal function have been undertaken starting with a variety of antiglucocorticoid agents. Several antiglucocorticoid drugs have been studied in depressed patients: including cortisol synthesis inhibitors such as metyrapone, aminoglutethimide, and ketoconazole. The glucocorticoid receptor antagonist mifepristone (RU486) has also been examined mostly in psychotic depression and, recently, there has been an effort to develop CRH receptor antagonists for clinical use.

With regard to ketoconazole, Murphy et al[120] reported six responders and two partial responders to ketoconazole in a case series of 10 patients with major depression who did not respond to standard antidepressants. Several case reports and small-open label studies have provided replication of these initial findings.[121-123] However, as with other cortisol synthesis inhibitors there is a lack of controlled trials with acceptable clinical trial methodology, although in the case of metyrapone, there is limited evidence for antidepressant effects in small placebo-controlled studies.[124,125]

Mifepristone (RU486) has also been studied as an antidepressant, primarily in the treatment of psychotic depression.[126,127] This compound is a competitive inhibitor of the glucocorticoid receptor. Mifepristone has been shown in small open as well as controlled studies to reduce psychotic symptoms in patients treated for major depression.[126,127] The therapeutic effect on depressive symptoms is not as substantial. The potential clinical utility of this treatment in this subgroup of depressed subjects who are generally more severely ill and more resistant to standard treatments requires further study.

In recent years there has been a substantial initiative to develop compounds which act as antagonists at the CRH1

Study	N	Melatonin dose (mg/day)	Duration	Design	Result
Carman et al, 1976[108]	6	Varying IV	Varying	Open	3/6 worse depression and sleep
DeVries and Peeters, 1997[109]	1	5	1 week	Case study	Improved depression
Fainstein et al, 1997[110]	9	3	3 weeks	Open	Improved sleep not depression
Dolberg et al, 1998[111]	19	5	4 weeks	RCT-adjunct to antidepressant	Improved sleep, not depression
Dalton et al, 2000[112]	8	10 (SR prep)	4 weeks	RCT-adjunct to antidepressant	Improved sleep, not depression
Serfaty et al, 2003[113]	38	6	4 weeks	Open	Depression improved with melatonin and placebo, trend for greater with melatonin
Bellipanni et al, 2005[114]	139	3	6 weeks	RCT	Melatonin>placebo for depression

Table VII. Melatonin treatment of depression.

receptor.[128,129] Given the overactivity of the adrenal axis in depression likely related to hypersecretion of CRH, there is a strong theoretical basis to such an approach. Several such compounds were discontinued early in drug development, due to unacceptable toxicity not necessarily related to their action at the CRH receptor.[127] There are limited data at this time on those compounds that have advanced to a later stage of development to determine whether this group of compounds may ultimately provide a novel class of antidepressants.[128,129]

Conclusion

Standard pharmacological treatment has proven to have limited efficacy in the treatment of major depression and related disorders. For example, up to half of patients treated for major depression will have an antidepressant response, and only approximately one third will achieve remission of symptoms.[130]

The relationship between endocrine dysfunction and depression has a long-established history. While psychiatric comorbidity is a common feature of many endocrine disorders, a specific, etiologically significant hormonal abnormality has been much more challenging to identify in major depression. Nonetheless, there has been a concerted effort to utilize hormonal treatments for patients with primary major depression, particularly those with illness refractory to standard treatment or where there are special circumstances to justify use, eg, the postpartum period or hypogonadal men. Our review confirms that results have been mixed and even a strong theoretical rationale does not necessarily ensure robust clinical findings. With most hormonal treatment studies, there have been methodological limitations, particularly small samples and a lack of randomized controlled trials. With the possible exception of tri-iodothyronine, few of these treatments have achieved even limited clinical utility and the potential of others, based on strong theoretical rationale, eg, CRH1 receptor antagonists, have yet to reveal their potential. Nonetheless, these studies, beside their potential clinical applicability, also provide important insight into the biological basis of mood disorders and the role of various hormonal systems in their etiology and treatment. ❑

REFERENCES

1. Loosen PT. Hormones of hypothalamic-pituitary-thyroid axis: a psychoneuroendocrine perspective. *Pharmacopsychiatry*. 1986;19:401-418.
2. Joffe RT, Levitt AJ. The thyroid and depression. In Joffe RT, Levitt AJ, eds. *The Thyroid Axis and Psychiatric Illness*. Washington, DC: American Psychiatric Press; 1993:195-254.
3. Griffiths EC. TRH: Endocrine and central effects. *Psychoneuroendocrinol*. 1985;10:225-235.
4. Kastin AJ, Ehrensinger H, Schalch DS, Anderson MS. Improvement in mental depression with decreased thyrotropin response after administration of thyrotropin-releasing hormone. *Lancet*. 1972;2:740-742.
5. Prange AJ Jr, Wilson IC, Lara BP, Lipton M. Effects of thyrotropin-releasing hormone and depression. *Lancet*. 1972;2:999-1001.
6. Coppen A, Montgomery S, Peet M. Bailey J, Marks V, Woods P. Thyrotropin-releasing hormone in the treatment of depression. *Lancet*. 1974;1:433-435.
7. Ehrsening RH, Kastin AJ, Schalch DS, Friesen HG, Vargas JR, Schally AV. Affective state and thyrotropin and prolactin responses after repeated imjections of thyrotropin-releasing hormone in depressed patients. *Am J Psychiatry*. 1974;131:714-718.
8. Hollister LE, Berger P, Ogle FL, Arnold RC, Johnson A. Protirelin (TRH) in depression. *Arch Gen Psychiatry*. 1974;31:468-470.
9. Mountjoy CQ, Price JS, Weller M, Hunter P, Hall R, Dewar JH. A double-blind cross-over sequential trial of oral thyrotropin-releasing hormone in depression. *Lancet*. 1974;2:958-960.
10. Van Den Burgh W, Van Praag HM, Bos ERH, Piers DA, Van Zanten AK, Doorenbos H. Thyrotropin releaSing hormone (TRH) as a possible quick acting but short lasting antidepressant. *Psychol Med*. 1975;5:404-412.
11. Furlong FW, Brown GM, Beeching MF. Thyrotropin-releasing hormone: differential antidepressant and endocrinological effects. *Am J Psychiatry*. 1976;133:1187-1190.
12. Kieley WF, Adrian AD, Lee JH. Nicoloff JT. Therapeutic failure of oral thyrotropin-releasing hormone in depression. *Psychosom Med*. 1976;38:233-241.
13. Van Den Burgh W, Van Praag HM, Bos ERH, Piers DA, van Zanten AK, Doorenbos H. TRH by slow, continuous infusion: an antidepressant? *Psychol Med*. 1976;6:393-397.
14. Vogel HP, Benkert O, Illig R, Müller-Oerlinghausen B, Poppenberg A. Psychoendocrinological and therapeutic effects of TRH in depression. *Acta Psychiatr Scand*. 1977;56:223-232.
15. Karlberg BE, Kjelman BF, Kagedel B. Treatment of endogenous depression with oral thyrotropin-releasing hormone and amitriptyline. *Acta Psychiatrica Scandinavica*. 1978;58:389-400.
16. Khan A, Mirolo MH, Lai H, et al. ECT and TRH: cholinergic involvement in a cognitive deficit state. *Psychopharmacol Bull*. 1993;29:345-352.
17. Chan BL, Singer W. The hypothalamic-pituitary-thyroid axis: Clinical and theoretical principles. In: Joffe RT, Levitt AJ, eds. *The Thyroid Axis and Psychiatric Illness.* Washington, DC: American Psychiatric Press;1993:147-165.
18. Prange AJ Jr, Wilson IC, Knox A, McClane TK, Lipton MA. Enhancement of imipramine by thyroid stimulating hormone: clinical and theoretical implications. *Am J Psychiatry*. 1970;127:191-199.
19. Falch FF, Celian CI, Rawson RW. Treatment of psychiatric disorders with triiodothyronine. *Am J Psychiatry*. 1958;124:341-348.
20. Feldemeisser-Reiss EE. The application of triiodothyronine in the treatment of mental disorders. *J Nerv Ment Dis*. 1958;127:540-546.
21. Prange AJ Jr, Wilson IC, Raybon AM, Lipton M. Enhancement of the imipramine antidepressant activity by thyroid hormone. *Am J Psychiatry*. 1969;126:457-465.
22. Wilson IC, Prange AJ Jr, McClane TK, Rabon AM, Lipton MA. Thyroid hormone enhancement of imipramine in non-retarded depression. *N Engl J Med*. 1970;282:1063-1067.
23. Coppen A, Whybrow PC, Noguera R. Maggs R, Prange AJ Jr. Comparative antidepressant value of L-tryptophan and imipramine with and without attempted potentiation by liothyronine. *Arch Gen Psychiatry*. 1972;26:234-24l.
24. Feighner J. P, King LJ, Schuckit MA, Croughan J, Briscoe, W. Hormonal potentiation of imipramine and ECT in primary depression. *Am J Psychiatry*. 1972;128:1230-1238.

Tratamiento hormonal de la depresión

Existe una relación bien reconocida entre las alteraciones de varios sistemas hormonales y los trastornos psiquiátricos, tanto en pacientes con patología endocrina como psiquiátrica. Esto ha promovido estudios clínicos e investigaciones que examinan la eficacia de diferentes hormonas para el tratamiento de la depresión. Se revisará la información disponible especialmente para las hormonas tiroideas, gonadales, pineales y de la corteza adrenal. Los datos aportan evidencias en general limitadas y de eficacia antidepresiva variable para estas hormonas.

Traitement hormonal de la dépression

Il existe une relation bien établie entre les variations des différents systèmes hormonaux et les troubles psychiatriques, à la fois chez les patients souffrant de troubles psychiatriques et ceux souffrant de troubles endocriniens. Ces constatations ont conduit la réalisation d'études cliniques et fondamentales afin d'analyser l'efficacité des différentes hormones dans le traitement de la dépression. Les données disponibles seront présentées, avec un intérêt particulier pour les hormones thyroïdiennes, gonadiques, épiphysaires et cortico-surrénaliennes. Les résultats apportent des arguments généralement limités et fluctuants en ce qui concerne l'efficacité de ces hormones.

25. Wheatley D. Potentiation of amitriptyline by thyroid hormone. *Arch Gen Psychiatry*. 1972;26:129.
26. Wilson IC, Prange AJ Jr, McLean TK, Rabon AM, Lipton M. Thyroid hormone enhancement of imipramine in non-retarded depressions. *N Engl J Med*. 1979;282:1653.
27. Earle BV. Thyroid hormone and tricyclic antidepressants in resistant depression. *Am J Psychiatry*. 1970;126:1667-1669.
28. Ogura C, Okuma T, Uchida Y, Imi S, Yogi H. Combined thyroid (triiodothyronine) tricyclic antidepressant treatment in depressive states. *Folia Psychiatr Neurol JPN*. 1974;28:179-186.
29. Banki CM. Triiodothyronine in the treatment of depression. *Orv Hetil*. 1975;116:2543.-2547.
30. Banki CM. Cerebrospinal fluid amine metabolytes after combined amitriptyline-tricyclic-thyronine treatment of depressed women. *Eur J Clin Pharmacol.* 1977;11:511-515.
31. Tsutsui S, Yamazaki Y, Naba T, Tsushima N. Combined therapy of T3 and antidepressants in depression. *J Int Med Res*. 1979;71:138-146.
32. Goodwin FK, Prange AJ, Post RM, Muscettola J, Lipton MA. Potentiation of antidepressant effects by l-triiodothyronine and tricyclic non-responders. *Am J Psychiatry*. 1982;139–154.
33. Schwarcz G, Halaris A, Baxter L, Escobar J, Thompson M, Young M. Normal thyroid function in zipromine non-responders converted to responders by the addition of l-triiodothyronine. *Am J Psychiatry*. 1984;141:1614-1616.
34. Gitlin MJ, Viner H, Fairbanks L, Hershman M, Ferifeld N. Failure of T3 to potentiate tricyclic antidepressant response. *J Affect Disord*. 1987;13:267-272.
35. Thase ME, Kupfer DG, Jarret DB. Treatment of imipramine resistant recurrent depression: I. An open clinical trial of adjunctive l-triiodothyronine. *J Clin Psychiatry*. 1989;50:385-388.
36. Joffe RT, Singer W. A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Res*. 1990;32:241-251.
37. Joffe RT, Singer W, Levitt AJ, McDonald C. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry*. 1993;50:387-391.
38. Birkenhäger TK, Vegt M, Nolen WA. An open study of triiodothyronine augmentation of tricyclic antidepressants in inpatients with refractory depression. *Pharmacopsychiatry*. 1997;1:23-26.
39. Agid O, Lerer B. Algorithm-based treatment of major depression in an outpatient seelinic: clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. *Int J Neuropsychopharmacol*. 2003;6:41-49.
40. Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. *J Affect Disord*. 2006;91:211-215.
41. Joffe RT, Sokolov ST, Levitt AJ. Lithium and triiodothyronine augmentation of antidepressants. *Can J Psychiatry*. 2006;51:791-793.
42. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. *Am J Psychiatry*. 2006;163:1519-1530.
43. Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. *Arch Gen Psychiatry*. 1996;53:842-848.
44. Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. *Int J Neuropsychopharmacol*. 2008;11:685-699.
45. Appelhof BC, Brouwer JP, van Dyck R, et al. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab*. 2004;89:6271-6276.
46. Cooper-Kazaz Are, Apter JT, Cohen R, et al. Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2007:64;679-688.
47. Posternak M, Novak S, Stern R, et al. A pilot effectiveness study: placebo-controlled trial of adjunctive L-triiodothyronine (T3) used to accelerate and potentiate the antidepressant response. *Int J Neuropsychopharmacol*. 2008;11:15-25.
48. Bauer MS, Hellweg R, Graf KJ, Baungartner A. Treatment of refractory depression with high-dose of thyroxine. *Neuropsychopharmacology*. 1998;18:444-448.
49. Spoov J, Lahdelma I. Should thyroid augmentation proceed lithium augmentation? A pilot study. *J Affect Disord*. 1998;49:235-241.
50. Rudas AS, Schmitz M, Pichler P, Baungartner A. Treatment of refractory chronic depression and dysthymia with high-dose thyroxine. *Biol Psychiatry*. 1999;45:229-235.
51. Lojko D, Rybakowski JK. L-thyroxine augmentation of serotonergic antidepressants in female patients with refractory depression. *J Affect Disord*. 2007;103:23-256.
52. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. *Psychoneuroendocrinology*. 2004;29:1071-1081.
53. Schmidt PJ, Berlin KL, Danaceau MA, et al. The effects of pharmacologically induced hypogonadism on mood in healthy men. *Arch Gen Psychiatry*. 2004;61:997-1004.
54. Anderson RA, Bancroft J, Wu FC. The effects of exogenous testosterone on sexuality and mood of normal men. *J Clin Endocrinol Metab*. 1992;75:1503-1507.

55. Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *J Androl*. 1992;13:297-304.
56. Luisi M, Franchi F. Double-blind group comparative study of testosterone undecanoate and mesterolone in hypogonadal male patients. *J Endocrinol Invest*. 1980;3:305-308.
57. Haren MT, Wittert GA, Chapman IM, Coates P, Morley JE. Effect of oral testosterone undecanoate on visuospatial cognition, mood and quality of life in elderly men with low-normal gonadal status. *Maturitas*. 2005;50:124-133.
58. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross CL. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab*. 1997;82:1661-1667.
59. Barrett-Connor E, von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo study. *J Clin Endocrinol Metab*. 1999;84:573-577.
60. Delhez M, Hansenne M, Legros JJ. Andropause and psychopathology: minor symptoms rather than pathological ones. *Psychoneuroendocrinology*. 2003;28:863-874.
61. Kanayama G, Hudson JI, Pope HG Jr. Long-term psychiatric and medical consequences of anabolic-androgenic steroid abuse: a looming public health concern? *Drug Alcohol Depend*. 2008;98:1-12.
62. Altschule M, Tillotson KJ. The use of testosterone in the treatment of depressions. *N Engl J Med*. 1948;239:1036-1038.
63. Barahal H. Testosterone in male involutional melancholia: preliminary report. *Psychiatr Q*. 1938;12:743-749.
64. Danziger L, Schroeder HT, Unger A. Androgen therapy for involutional melancholia. *Arch Neurol Psychiatry*. 1944;51:457-461.
65. Davidoff E, Goodstone G. Use of testosterone propionate in treatment of involutional psychosis in the male. *Arch Neurol Psychiatry*. 1942;48:811-817.
66. Seidman SN, Rabkin JG. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. *J Affect Disord*. 1998;48:157-161.
67. Seidman SN, Spatz E, Rizzo C, Roose SP. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry*. 2001;62:406-412.
68. Perry PJ, Yates WR, Williams RD, et al. Testosterone therapy in late-life major depression in males. *J Clin Psychiatry*. 2002;63:1096-1101.
69. Pope HG Jr, Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2003;160:105-111.
70. Orengo CA, Fullerton L, Kunik ME. Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. *J Geriatr Psychiatry Neurol*. 2005;18:20-24.
71. Seidman SN, Miyazaki M, Roose SP. Intramuscular testosterone supplementation to selective serotonin reuptake inhibitor in treatment-resistant depressed men: randomized placebo-controlled clinical trial. *J Clin Psychopharmacol*. 2005;25:584-588.
72. Seidman SN, Orr G, Raviv G, et al. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. *J Clin Psychopharmacol*. 2009;29:216-221.
73. Shores M, Kivlahan DR, Sadak TI, Li EJ, Matsumoto AM. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *J Clin Psychiatry*. 2009;70:1009-1016.
74. Pope, HG, Amiaz, R, Brennan B, et al. Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. *J Clin Psychopharmacol*. 2010;30:126-134.
75. Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. *Eur Urol*. 2006;50:935-939.
76. Morgentaler A. New concepts regarding the relationship of testosterone and prostate cancer. *Future Oncol*. 2007;3:123-126.
77. Christian CA, Moenter SM. The neurobiology of preovulatory and estradiol-induced gonadotropin-releasing hormone surges. *Endocr Rev*. 2010;4:544-577.
78. Moenter SM, Chu Z, Christian CA. Neurobiological mechanisms underlying oestradiol egative and positive feedback regulation of gonadotrophin-releasing hormone neurones. *J Neuroendocrinol*. 2009;4:327-333.
79. Biagini G, Panuccio G, Avoli M. Neurosteroids and epilepsy. *Curr Opin Neurol*. 2010;3:170-176.
80. Studd J, Panay N. Are oestrogens useful for the treatment of depression in women? *Best Pract Res Clin Obstetr Gynaecol*. 2009;23:63-71.
81. Wittchen HU, Becker E, Lieb R, Krause P Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychol Med*. 2002;32:119-132.
82. MacQueen G, Chokka P. Special issues in the management of depression in women. *Can J Psychiatry*. 2004;49(suppl 1):27S-40S.
83. Usman SB, Indusekhar R, O'Brien S. Hormonal management of premenstrual syndrome *Best Pract Res Clin Obstet Gynaecol*. 2008;22:251-260.
84. Yonkers KA, O'Brien PM, Eriksson E Premenstrual Syndrome. *Lancet*. 2008;371:1200-1210.
85. Tommaselli GA, Di Carlo C, Bifulco G, Di Spiezio Sardo A, Pellicano M, Nappi C. Serum leptin levels in patients with premenstrual syndrome treated with GnRH analogues alone and in association with tibolone. *Clin Endocrinol (Oxf).* 2003;59:716-722.
86. Mortola JF. Applications of gonadotropin-releasing hormone analogues in the treatment of premenstrual syndrome. *Clin Obstet Gynecol*. 1993;36:753-763.
87. Rapkin A. A review of treatment of premenstrual syndrome and premenstrual dysphoric disorder. *Psychoneuroendocrinol*. 2003; 28(suppl 3):39–53.
88. Freeman EW, Kroll R, Rapkin A, et al; PMS/PMDD Research Group. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based Med*. 2001;10:561–569.
89. Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res*. 1992;36:257–266.
90. Dickerson V. Quality of life issues. Potential role for an oral contraceptive containing ethinyl estradiol and drosperinone. *J Reprod Med*. 2002;47(suppl 11): 985–993.
91. Hahn PM, Van Vat DA, Reid RL. A randomised, placebo-controlled crossover trail of danazol for the treatment of premenstrual syndrome. *Psychoneuroendocrinology*. 1995; 20:193–209.
92. Halbriech U, Rojansky N, Palter S. Elimination of ovulation and menstrual cyclicity (with danazol) improves dysphoric premenstrual syndrome. *Fertil Steril*. 1991;56:1066–1069.
93. O'Brien PMS, Aukhalil IED. Randomised controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol*. 1999;180:18–23.
94. Sichel DA, Cohen LS, Robertson LM, Ruttenberg A, Rosenbaum JF. Prophylactic estrogen in recurrent postpartum affective disorder. *Biol Psychiatry*. 1995;38:814-818.
95. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet*. 1996 347:930-933.
96. Schmidt, P. Rubinow, DR. Sex hormones and mood in the perimenopause. *Ann N Y Acad Sci*. 2009:1179:70–85.
97. Schneider L, Small G, Hamilton S, Bystritsky A, Nemeroff C, Meyers B. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. *Am J Geriatr Psychiatry*. 1997;5:97–106.
98. Soares C, Poitras J, Prouty J, Alexander A, Shifren J, Cohen L. Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. *J Clin Psychiatry*. 2003;64:473–479.
99. Schneider L, Small G, Clary C. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am J Geriatr Psychiatry*. 2001;9:393–399.
100. Amsterdam J, Garcia-Espana F, Fawcett J, et al. Fluoxetine efficacy in menopausal women with and without estrogen replacement. *J Affect Disord.* 1999;55:11–17.
101. Schmidt P, Nieman L, Danaceau M, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol*. 2000;183:414–420.
102. Wetterberg L. Melatonin in humans: physiological and clinical studies. *J Neural Transm*. 1978;13(suppl):389–410.

103. Wirz-Justice A. Biological rhythm disturbances in mood disorders. *Int Clin Psychopharmacol*. 2006;21(suppl 1):S11–S15.
104. Brown G, Singer W, Joffe R. Lack of association between thyroid and pineal responses to antidepressant treatment. *Depression*. 1996;4:73–76.
105. Sack RL, Brandes BS, Kendall BS, Lewy AJ. Entrainment of freerunning circadian rhythms by melatonin in blind people. *N Engl J Med*. 2000;343:1070–1077.
106. Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of winter depression: a pilot study. *Psychiatry Res*. 1997;77:57–61.
107. Rosenthal NE, Sack DA, James SP, Parry BL, Mendelson WB, Tamarkin L. Seasonal affective disorder and phototherapy. *Ann NY Acad Sci*. 1985;453:260–269.
108. Carman JS, Post RM, Buswell R, Goodwin FK. Negative effects of melatonin on depression. *Am J Psychiatry*. 1976;133:1181–1186.
109. De Vries MW, Peeters FPML. Melatonin as a therapeutic agent in the treatment of sleep disturbance in depression. *J Nerv Ment Dis*. 1997;185:201–202.
110. Fainstein I, Bonetto AJ, Brusco LI, Cardinali DP. Effects of melatonin in elderly patients with sleep disturbance: a pilot study. *Curr Ther Res*. 1997;58:990–1000.
111. Dolberg OT, Hirschmann S, Grunhaus L Melatonin for the treatment of sleep disturbances in major depression. *Am J Psychiatry*. 1998;155:1119–1121.
112. Dalton EJ, Rotondi D, Levitan RD, Kennedy SH, Brown GM. Use of slow release melatonin in treatment resistant depression. *J Psychiatry Neurosci*. 2000;25:48–52.
113. Serfaty MA, Osborne D, Buszewicz MJ, Raven PW. The effect of exogeneous melatonin in major depression. *Chronobiol Int*. 2003;20:1191–1192.
114. Bellipanni GFDIM, Blasi F, Di Marzo A Effects of melatonin in perimenopausal and menopausal women: our personal experience. *Ann N Y Acad Sci*. 2005;1057:393–402.
115. Kasper S, Hajak G ,Wulff K. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. *J Clin Psychiatry*. 2010;71:109-120.
116. Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatonergic agonist and selective 5HT2c antagonistic, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol*. 2002;17:239-247.
117. Kling MA, Coleman VH, Schulkin J. Glucocorticoid inhibition in the treatment of depression: can we think outside the endocrine hypothalamus? *Depress Anxiety*. 2009;26:641-649.
118. Lemoine P, Guilleminault C, Alvarez E. Improvement of subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry*. 2007;68:1723-1732.
119. Hale A, Corral RM, Mencacci C, Ruiz JS, Severo CA, Gentil V. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. *Int Clin Psychopharmacol*. 2010;25:305–314.
120. Murphy BE. Treatment of major depression with steroid suppressive drugs. *J Steroid Biochem Mol Biol*. 1991;39:239–244.
121. Ghadirian AM, Englesmann F, Dhar V, et al. The psychotropic effects of inhibitors of steroid biosynthesis in depressed patients refractory to treatment. *Biol Psychiatry*. 1995;37:369–375.
122. Wolkowitz OM, Reus VI, Chan T Manfredi F, Raum W, Johnson R, Canick J. Antiglucocorticoid treatment of depression: double-blind ketoconazole. *Biol Psychiatry*. 1999;45:1070–1074.
123. Thakore JH, Dinan T. Cortisol synthesis inhibition: a new treatment strategy for the clinical and endocrine manifestations of depression. *Biol Psychiatry*. 1995;37:364–368.
124. O'Dwyer AM, Lightman SL, Marks MN, Checkley SA. Treatment of major depression with metyrapone and hydrocortisone. *J Affect Disord*. 1995;33:123–128.
125. Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K. Metyrapone as additive treatment in major depression: a double-blind and placebocontrolled trial. *Arch Gen Psychiatry*. 2004;61:1235–1244.
126. Flores BH, Kenna H, Keller J, Solvason HB, Schatzberg AF. Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology*. 2006;31:628-636.
127. DeBattista C, Belanoff J. The use of mifepristone in the treatment of neuropsychiatric disorders. *Trends Endocrinol Metab*. 2006;17:117-121.
128. Holsboer F, Ising M. Central CRH system in depression and anxiety--evidence from clinical studies with CRH1 receptor antagonists. *Eur J Pharmacol.* 2008;583:350-357.
129. Holsboer F. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. *J Psychiatr Res*. 1999;33:181-214.
130. Rush AJ, Trivedi MH, Wisniewski SR, et al; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354:1231-1242.