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:

- **Thyroid hormones**
- **Gonadal steroids, which include testosterone in men and gonadal steroids in women**
- **Melatonin**
- **Adrenal cortex hormones**

Disorders of the thyroid axis have been closely linked to psychiatric disorders. While hyperthyroidism may present with a heterogenous range of psychiatric symptoms and syndromes, clinical hypothyroidism is invariably
associated with depressive symptoms. Although extensive research has shown that the vast majority of patients who present with major depression are euthyroid, 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. 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 and by oral routes for depression. TRH has been administered intravenously either as a single dose or as several doses over 3 to 4 days, and transient antidepressant effects have been demonstrated. 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. 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.

**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. One study to date has examined the antidepressant effect of TSH. Prange and collaborators 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). T4 is the major secretory product of the thyroid, and most T4 undergoes peripheral conversion to T3 in order to exert its physiological action. 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. In early studies, T3 was used as monotherapy for the treatment of depressed patients. 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 samples.

| 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 used T3 to accelerate the response to tricyclic antidepressants. In several studies, 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. 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

**Table II.** T3 acceleration of antidepressant response.

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

**Table III.** T3 augmentation of antidepressants.

| Study                  | N  | T3 dose (μg/day) | Design                  | Result                          |
|------------------------|----|-----------------|-------------------------|--------------------------------|
| Earle, 1970            | 25 | 25              | Open                    | 14 of 25 responded              |
| Ogura et al, 1974      | 44 | 20-30           | Open                    | 29 of 44 responded              |
| Banki, 1975            | 52 | 20-40           | Open                    | 39 of 52 responded              |
| Banki, 1977            | 33 | 20              | Partially controlled    | 23 of 33 responded              |
| Tsutsui et al, 1979    | 11 | 5-25            | Open                    | 10 of 11 responded              |
| Goodwin et al, 1982    | 12 | 25-50           | Double-blind            | 8 of 12 responded               |
| Schwarze et al, 1984   | 8  | 25-50           | Open                    | 4 of 8 responded                |
| Gitlin et al, 1987     | 16 | 25              | Double-blind, crossover | T3 = placebo                    |
| Thase et al, 1989      | 20 | 25              | Open                    | 5 of 20 responded               |
| Joffe and Singer, 1990 | 38 | 37.5            | Double-blind            | 9 of 17 responded               |
| Joffe et al, 1993      | 51 | 37.5            | Double-blind, placebo-controlled | 10 of 17 responded to T3, T3 > placebo, T3 = (lithium?) |
| Birkenhager et al, 1997| 14 | 37.5            | Open                    | No response—all inpatients      |
| Agid & Lerer, 2003     | 74 | 25-50           | Open, added to SSRI     | 44/74 responded at 4 weeks      |
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, 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. 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 (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. 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, 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 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 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 study showing a trend toward acceleration. As far as enhancement of SSRI response is concerned, the data are conflicting, with one positive, one negative, and one trending study. 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.

### Table IV. T3 Enhancement of antidepressants.

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

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

| Study                        | N   | Patients                   | T4 Dose (μg/day) | Design              | Response                      |
|------------------------------|-----|----------------------------|-----------------|---------------------|-------------------------------|
| Joffe and Singer, 1990       | 38  | Unipolar major depression  | 150             | Double-blind vs T3 | 4 of 21 responded to T4, T4 < T3 |
| Bauer et al, 1998            | 17  | Unipolar (or) bipolar depression | 300-500       | Open                | 10 of 17 showed full or partial response |
| Spoov and Lahdelma, 1998     | 22  | Major depression           | 200             | Crossover vs lithium | T4 > lithium                  |
| Rudas et al, 1999            | 9   | Chronic depression and dysthymia | 150-300       | Open                | 6 of 9 full or partial response |
| Lojko and Rybakowski, 2007   | 17  | Unipolar and bipolar depression | 100             | Open, on SSRI      | 11 remission and 16 response  |
These studies generally involve open designs using various diagnoses, including both unipolar and bipolar subjects in one study\(^6\) and chronic depression or dysthmic patients in another study.\(^9\) 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.\(^62,63\) 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.\(^66,67\) 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. 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). 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. Hormonal therapy of premenstrual symptoms involves suppression of ovulation by using oral contraceptives, 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. GnRH agonists have been shown to be variably effective in reducing psychiatric morbidity in several placebo-controlled trials. For the most part these studies have varying methodological limitations. In addition, side-effect burden is a problem with the GnRH agonists, particularly those relating to hypostrogenism which are only partially ameliorated by add-back estrogen and progestogen therapy. The reduction in bone mass with these compounds limits duration of treatment to no more than 6 to 9 months. 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. 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. 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. However, its androgenic side effects, particularly masculinization, as well as

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

**Table VI. Testosterone treatment of depression.**
adverse effects on liver function and lipid parameters, seriously limits its clinical utility.95-97

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.98,99 In the open trial, 21 of 23 postpartum severely depressed women responded to sublingual 17b-estradiol (4.8 mg/d) for 8 weeks.100 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.96

Perimenopausal/postmenopausal period

During this life phase, there is an increasingly erratic cyclic variation in estrogen and progesterone 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,99-101 estrogen has been shown to reduce both physical and depressive symptoms. In particular, two of three recent controlled trials99-101 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.45-101 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.93-101 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.102 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.103

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.103,104 In seasonal depression, the first report actually demonstrated worsening of depressive symptoms in a study of 5 depressed subjects given intravenous melatonin at varying but usually high doses.105 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 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. 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. 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. Approximately half of all severely depressed subjects have elevated levels of cortisol, and depression is a frequent complication of both Cushing’s syndrome as well as with longer-term treatment with exogenous corticosteroids. 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. 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 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. 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.

Mifepristone (RU486) has also been studied as an antidepressant, primarily in the treatment of psychotic depression. 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. 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

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**Table VII. Melatonin treatment of depression.**

| Study                | N    | Melatonin dose (mg/day) | Duration | Design       | Result                                           |
|----------------------|------|------------------------|----------|--------------|-------------------------------------------------|
| Carman et al, 1976   | 6    | Varying IV             | Varying  | Open         | 3/6 worse depression and sleep                  |
| DeVries and Peeters, 1997 | 1    | 5                      | 1 week   | Case study   | Improved depression                             |
| Fainstein et al, 1997 | 9    | 3                      | 3 weeks  | Open         | Improved sleep not depression                   |
| Dolberg et al, 1998  | 19   | 5                      | 4 weeks  | RCT-adjunct to antidepressant | Improved sleep, not depression                  |
| Dalton et al, 2000   | 8    | 10 (SR prep)           | 4 weeks  | RCT-adjunct to antidepressant | Improved sleep, not depression                  |
| Serfaty et al, 2003  | 38   | 6                      | 4 weeks  | Open         | Depression improved with melatonin and placebo, trend for greater with melatonin |
| Bellipanni et al, 2005 | 139  | 3                      | 6 weeks  | RCT          | Melatonin>placebo for depression                |
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.\(^\text{127}\) There are limited data at this time on those compounds that have arrived at a later stage of development to determine whether this group of compounds may ultimately provide a novel class of antidepressants.\(^\text{128,129}\)

**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.\(^\text{130}\) 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.

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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 coroetra 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 soufrant de troubles endocriniens. Ces constatations ont conduit à 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, éphiphysaires et cortico-surrénaliennes. Les résultats apportent des arguments généralement limités et fluctuants en ce qui concerne l'efficacité de ces hormones.
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Pharmacological aspects

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