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(54) **METHODS FOR TREATING STRESS DISORDERS USING GLUCOCORTICOID RECEPTOR-SPECIFIC ANTAGONISTS**

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(58) **Field of Search** 514/178, 179

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(57) **ABSTRACT**

This invention generally pertains to the field of psychiatry. In particular, this invention pertains to the discovery that agents which inhibit the binding of cortisol to its receptors can be used in methods for treating stress disorders. Mifepristone, a potent specific glucocorticoid receptor antagonist, can be used in these methods. The invention also provides a kit for treating stress disorders in a human including a glucocorticoid receptor antagonist and instructional material teaching the indications, dosage and schedule of administration of the glucocorticoid receptor antagonist.

16 Claims, No Drawings

METHODS FOR TREATING STRESS DISORDERS USING GLUCOCORTICOID RECEPTOR-SPECIFIC ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. patent application Ser. No. 60/278,523 filed Mar. 23, 2001, which is explicitly incorporated herein by reference in its entirety and for all purposes.

FIELD OF THE INVENTION

This invention generally pertains to the field of psychiatry. In particular, this invention pertains to the discovery that agents which inhibit the binding of cortisol to the glucocorticoid receptor can be used in methods of treating stress related disorders.

INTRODUCTION

Stress disorders are environmentally induced psychiatric conditions. Exposure to one or more traumatic stressful events can lead to acute or extended periods in which the victim experiences dissociative symptoms and re-experiences the traumatic event. In some individuals, exposure to traumatic stressors can even induce brief episodes of mental dysfunction and disorganization so severe as to be classified as psychotic. While antidepressant drugs such as selective serotonin reuptake inhibitors, tricyclics, and monoamine oxidase inhibitors have shown promise in trials against Post-Traumatic Stress Disorder, there is no currently available pharmacotherapy generally effective against stress disorders in general or in mixed patient populations. See Marshall & Pierce, *Harvard Rev Psychiatry* 7:247–55 (2000).

Cortisol, which is secreted in response to ACTH (corticotropin), shows circadian rhythm variation, and further, is an important element in responsiveness to many physical and psychological stresses. It has been proposed that, with age, the cortisol regulatory system becomes hyperactivated in some individuals, resulting in hypercortisolemia. It has additionally been postulated that high levels of cortisol are neurotoxic, particularly in the hippocampus, a brain structure that is thought to be central to the processing and temporary storage of complex information and memory (see, e.g., Sapolsky et al., *Ann. NY Acad. Sci.* 746:294–304, 1994; Silva, *Annu. Rev. Genet.* 31:527–546, 1997; de Leon et al., *J. Clin. Endocrinol & Metab.* 82:3251, 1997; Maeda et al., supra).

Persistent high levels of circulating cortisol are associated with loss of volume in the hippocampus. See Starkman et al., *Biol Psychiatry* 32:756–764, 1992. Moreover, surgical treatment of the adrenal glands to reduce excessive cortisol secretion can reverse the hippocampal atrophy caused by high cortisol levels. See Starkman et al., *Biol Psychiatry* 46:1595–602, 1999. Hippocampal atrophy is also a characteristic of Post-Traumatic stress disorder, and there is evidence to suggest that elevated levels of glucocorticoids associated with stress disorders contribute to loss of hippocampal volume. See Sapolsky, *Arch Gen Psychiatry* 57:925–935 (2000).

Despite the association between stress and cortisol secretion, evidence has accumulated that many patients suffering from persistent stress disorders have lowered, rather than elevated, cortisol levels. See Heim et al., *Psychoneuroendocrinology* 25:1–25 (2000). Hypocortisolism in stress disorder patients may be reconciled with the elevated cortisol levels brought about by acute stress by assuming that persistent stress disorders represent a persistent state of cortisol hypersensitivity. That is, exposure to acute stressors may trigger negative feedback mechanisms that ultimately lead to decreased cortisol secretion. Persistently low levels of cortisol may leave the hypothalamic-pituitary-adrenal axis 'primed' to respond to even minor elevations in circulating glucocorticoid levels. As a result, minor stressors—resulting in small elevations in glucocorticoid levels—can provoke traumatic responses in patients suffering from persistent stress disorders. See Yehuda, *J Clin Psychiatry* 61 Suppl 7(5):14–21 (2000).

There has been no evidence prior to this invention, however, that a glucocorticoid receptor antagonist can be an effective treatment for stress disorders, especially in patients having cortisol levels that fall within a normal range. Many of the actions of cortisol are mediated by binding to the type I (mineralocorticoid) receptor, which is preferentially occupied, relative to the type II (glucocorticoid) receptor, at physiological cortisol levels. As cortisol levels increase, more glucocorticoid receptors are occupied and activated. Because cortisol plays an essential role in metabolism, inhibition of all cortisol-mediated activities, however, would be fatal. Therefore, antagonists that specifically prevent glucocorticoid receptor functions, but do not antagonize mineralocorticoid receptor functions are of particular use in this invention. Mifepristone and similar antagonists are examples of this category of receptor antagonists.

Mifepristone has been noted as being effective at abrogating some of the age-associated electrophysiological changes in the rat hippocampus (Talmi et al., *Neurobiol. of Aging* 17:9–14, 1996) and also as providing protection against oxidative stress-induced neuronal cell death in the mouse hippocampus (Behl et al., *European J. of Neuorsci.* 9:912–920, 1997). There have been no studies, however, that have shown that mifepristone can forestall or reverse the loss of hippocampal atrophy associated with stress disorders.

The present inventor has determined that glucocorticoid receptor antagonists such as mifepristone are effective agents for the specific treatment of stress disorders in patients with normal or decreased cortisol levels. The present invention therefore fulfills the need for an effective treatment for stress disorders by providing methods of administering glucocorticoid receptor antagonists to treat patients diagnosed with stress disorders.

SUMMARY OF THE INVENTION

The invention provides a method of ameliorating the symptoms of a stress disorder in a patient who has normal or decreased cortisol levels. The method comprises administration of a therapeutically effective amount of a glucocorticoid receptor antagonist to the patient, who may be diagnosed with Post-Traumatic Stress Disorder, Acute Stress Disorder, or Brief Psychotic Disorder with Marked Stressor (s).

In one embodiment of the invention, the method of treating a stress disorder uses a glucocorticoid receptor antagonist comprising a steroidal skeleton with at least one phenyl-containing moiety in the 11-beta position of the steroidal skeleton. The phenyl-containing moiety in the 11-beta position of the steroidal skeleton can be a dimethylaminophenyl moiety. In alternative embodiments, the glucocorticoid receptor antagonist comprises mifepristone, or,

the glucocorticoid receptor antagonist is selected from the group consisting of RU009 and RU044.

In other embodiments, the glucocorticoid receptor antagonist is administered in a daily amount of between about 0.5 to about 20 mg per kilogram of body weight per day; between about 1 to about 10 mg per kilogram of body weight per day; or between about 1 to about 4 mg per kilogram of body weight per day. The administration can be once per day. In alternative embodiments, the mode of glucocorticoid receptor antagonist administration is oral, or by a transdermal application, by a nebulized suspension, or by an aerosol spray.

The invention also provides a method of preventing, delaying, or lessening the emergence of stress disorder symptoms in a patient who has been exposed to a traumatic stressor, but who has not yet developed the characteristic symptoms of a stress disorder. The method comprises administering an effective amount of a glucocorticoid receptor antagonist to the patient within 30 days of exposure to a traumatic stressor.

The invention also provides a kit for the treatment of a stress disorder in a human, the kit comprising a glucocorticoid receptor antagonist; and, an instructional material teaching the indications, dosage and schedule of administration of the glucocorticoid receptor antagonist. In alternative embodiments, the instructional material indicates that the glucocorticoid receptor antagonist can be administered in a daily amount of about 0.5 to about 20 mg per kilogram of body weight per day, of about 1 to about 10 mg per kilogram of body weight per day, or about 1 to about 4 mg per kilogram of body weight per day. The instructional material can indicate that cortisol contributes to the stress-induced symptoms in patients with stress disorders, and that the glucocorticoid receptor antagonist can be used to treat stress disorders. In one embodiment, the glucocorticoid receptor antagonist in the kit is mifepristone. The mifepristone can in tablet form.

A further understanding of the nature and advantages of the present invention is realized by reference to the remaining portions of the specification and claims.

All publications, patents and patent applications cited herein are hereby expressly incorporated by reference for all purposes.

DEFINITIONS

The term "treating" refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the methods of the invention success fully treat a patient's stress disorders by decreasing the incidence of dissociative symptoms, re-experience of traumatic events, or psychotic behavior.

The term "stress disorder" refers to a psychiatric condition precipitated by exposure to a traumatic or stressful event. Stress disorders include Acute Stress Disorder, Post-Traumatic Stress Disorder, and Brief Psychotic Disorder with Marked Stressor(s).

The term "Acute Stress Disorder" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, D.C., 2000 ("DSM-IV-TR"). The DSM-IV-TR defines "Acute Stress Disorder" as characterized by anxiety, dissociative, and other symptoms occurring within 1 month after exposure to an extreme traumatic stressor. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Acute Stress Disorder.

The term "Post-Traumatic Stress Disorder" refers to a psychiatric condition in its broadest sense, as defined in DSM-IV-TR. The DSM-IV-TR defines "Post-Traumatic Stress Disorder" as characterized by persistent re-experiencing of an extreme traumatic event. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Post-Traumatic Stress Disorder.

The term "Brief Psychotic Disorder with Marked Stressor(s)" refers to a psychiatric condition in its broadest sense, as defined in DSM-IV-TR. The DSM-IV-TR defines "Brief Psychotic Disorder with Marked Stressor(s)" as a sudden but brief onset of psychotic symptoms developing shortly after and apparently in response to one or more stressful events. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Brief Psychotic Disorder with Marked Stressor(s).

The term "cortisol" refers to a family of compositions also referred to hydrocortisone, and any synthetic or natural analogues thereof.

The term "glucocorticoid receptor" ("GR") refers to a family of intracellular receptors also referred to as the cortisol receptor, which specifically bind to cortisol and/or cortisol analogs. The term includes isoforms of GR, recombinant GR and mutated GR.

The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or 11-beta-(4dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the GR, typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Chemical names for RU-486 vary; for example, RU486 has also been termed: 11B-[p-(Dimethylamino)phenyl] -17B-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one; 11B-(4-dimethyl-aminophenyl)-17B-hydroxy-17A-(prop-1-ynyl)-estra-4,9-dien-3-one; 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1l)-estra-4,9-diene-3-one; 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-E;(11B,17B)-11-[4-dimethylamino)-phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11B-[4-(N,N-dimethylamino)phenyl] -17A-(prop-1-ynyl)-D-4,9-estradiene-17B-ol-3-one.

The term "specific glucocorticoid receptor antagonist" refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to a GR. A "specific glucocorticoid receptor antagonist" also refers to any composition or compound which inhibits any biological response associated with the binding of a GR to an agonist. By "specific", we intend the drug to preferentially bind to the GR rather than the mineralocorticoid receptor (MR) at a rate of at least 100-fold, and frequently 1000-fold.

A patient "not otherwise in need of treatment with a glucocorticoid receptor antagonist" is a patient who is not suffering from a condition which is known in the art to be

effectively treatable with glucocorticoid receptor antagonists. Conditions known or reported in the art to be effectively treatable with glucocorticoid receptor antagonists include Cushing's disease, schizophrenia and mania, dementia, delirium, and psychotic major depression.

DETAILED DESCRIPTION OF THE INVENTION

This invention pertains to the surprising discovery that agents that can inhibit glucocorticoid receptor-mediated biological responses are effective for treating stress disorders. In treating stress disorders, the methods of the invention can preferably relieve the symptoms of a stress disorder or lead to complete resolution of the underlying disorder itself In one embodiment, the methods of the invention use agents that act as glucocorticoid receptor (GR) antagonists, blocking the interaction of cortisol with GR, to treat or ameliorate a stress disorder or symptoms associated with a stress disorder. The methods of the invention are effective in ameliorating the symptoms of a stress disorder patient afflicted with either decreased, normal or increased levels of cortisol or other glucocorticoids, natural or synthetic.

Cortisol acts by binding to an intracellular, glucocorticoid receptor (GR). In man, glucocorticoid receptors are present in two forms: a ligand-binding GR-alpha of 777 amino acids; and, a GR-beta isoform that differs in only the last fifteen amino acids. The two types of GR have high affinity for their specific ligands, and are considered to function through the same transduction pathways.

The biologic effects of cortisol, including pathologies or dysfunctions caused by hypercortisolemia, can be modulated and controlled at the GR level using receptor antagonists. Several different classes of agents are able to act as GR antagonists, i.e., to block the physiologic effects of GR-agonist binding (the natural agonist is cortisol). These antagonists include compositions which, by binding to GR, block the ability of an agonist to effectively bind to and/or activate the GR. One family of known GR antagonists, mifepristone and related compounds, are effective and potent anti-glucocorticoid agents in humans (Bertagna, *J. Clin. Endocrinol. Metab.* 59:25, 1984). Mifepristone binds to the GR with high affinity, with a K of dissociation $<10^{-9}$ M (Cadepond, *Annu. Rev. Med.* 48:129, 1997). Thus, in one embodiment of the invention, mifepristone and related compounds are used to treat stress disorders.

Stress disorders typically manifest themselves with a variety of symptoms, including purely psychological symptoms such as re-experiencing traumatic events, physiological reactions such as persistent arousal, and psychiatric symptoms such as psychotic delusions. Thus, a variety of means of diagnosing stress disorders and assessing the success of treatment, i.e., the success and extent the symptoms of stress disorders are lessened by the methods of the invention, can be used, and a few exemplary means are set forth herein. These means can include classical, subjective psychological evaluations and neuropsychiatric examinations as described below.

As the methods of the invention include use of any means to inhibit the biological effects of an agonist-bound GR, illustrative compounds and compositions which can be used to treat stress disorders are also set forth. Routine procedures that can be used to identify further compounds and compositions able to block the biological response caused by a GR-agonist interaction for use in practicing the methods of the invention are also described. As the invention provides for administering these compounds and compositions as pharmaceuticals, routine means to determine GR antagonist drug regimens and formulations to practice the methods of the invention are set forth below.

1. Diagnosis of Acute Stress Disorder

Acute Stress Disorder (ASD) is characterized by a constellation of symptoms, lasting at least two days, that appear and resolve within one month of exposure to an extreme traumatic stressor. If symptoms appear or persist beyond one month after exposure to the traumatic stressor, the patient may be considered to suffer from Post-Traumatic Stress Disorder rather than ASD. ASD is a common precursor to Post-Traumatic Stress Disorder, and up to 80% of trauma survivors initially suffering from ASD will meet the diagnostic criteria for Post-Traumatic Stress Disorder six months later (see Brewin et al., *Am J Psychiatry* 156:360–6, 1999).

Patients develop ASD following exposure to an extreme traumatic stressor (DSM-IV-TR Criterion A). A person must respond to the stressor with intense fear, helplessness, or horror to be diagnosed with ASD. ASD may develop from direct experience of traumatic events, including violent crimes, physical trauma, combat, diagnosis with a life-threatening illness, and natural or manmade disasters. Patients may also develop ASD from witnessing or learning about traumatic events that happen to others, especially family members or close friends. Unexpected exposure to death, dead bodies, or body parts may also induce ASD.

A diagnosis of ASD requires that the person meet several other symptomatic criteria. The person must experience three or more dissociative symptoms in connection with the traumatic stressor (Criterion B). Dissociative symptoms include a subjective sense of numbing or detachment, a reduction in awareness of surroundings, derealization, depersonalization, and dissociative amnesia. Furthermore, ASD requires that the victim persistently re-experience the traumatic event, though recurrent images, thoughts, dreams, illusions, flashbacks, sense of reliving the event, or distress upon exposure to reminders of the event (Criterion C). The person must display marked avoidance of stimuli that arouse recollection of the trauma (Criterion D) and marked symptoms of anxiety or increased arousal (Criterion E). Finally, in addition to the time requirements described above, a diagnosis of ASD requires that the disturbance cause significant distress; or life impairment, and not be due to another psychiatric or physiological condition (Criteria F-H).

ASD may be diagnosed and evaluated with any one of several objective, standardized test instruments known in the art, although skilled clinicians may readily diagnose ASD through unstructured clinical interactions. Standardized test instruments are constructed by experienced clinical researchers based on DSM diagnostic criteria, and are typically validated through statistical studies and comparisons of various patient populations. Generally, standardized instruments assess both manifest psychological or physiological symptoms as well as internal thought processes. Standardized test instruments may comprise structured clinical interviews that are administered by a health care practitioner, or they may comprise self-reporting questionnaires that are completed by the putative patient. Either clinician-administered or self-reported test instruments may be used to identify ASD patients who will benefit from anti-glucocorticoid therapy.

Guidance, procedures and recommendations for test instruments used to diagnose stress disorders may be found in *Standards of Traumatology Practice,* April 2000 revision (Academy of Traumatology, Tallahassee, Fla.). Clinician-

administered test instruments for suitable for identifying patients in need of anti-glucocorticoid therapy for ASD include the Acute Stress Disorder Interview (ASDI; Bryant et al., *Psychological Assessment* 10:215–20 (1998)). Self-reported instruments include the modified Stanford Acute Stress Reaction Questionnaire (SASRQ; Cardena et al., *J Traumatic Stress* 13:719–734 (2000)) and the Acute Stress Disorder Scale (ASDS; Bryant et al., *Psychological Assessment* 12:61–68 (2000)). Cutoff scores yielding the most statistically valid division of patients into ASD and non-ASD populations have been established and reported for each test (e.g., a score of 9 or greater for the dissociative cluster and 28 or greater on the reexperiencing, avoidance, and arousal clusters for the ASDS) and may be used to select patients for anti-glucocorticoid therapy.

2. Diagnosis of Post-Traumatic Stress Disorder

Like Acute Stress Disorder, Post-Traumatic Stress Disorder (PTSD) emerges following exposure to an extreme traumatic stressor, and is characterized by persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, and anxiety or increased arousal. The types of traumatic stressors giving rise to PTSD, and the manifestations of PTSD symptoms, are identical to those described above for ASD, but for three differences. First, the dissociative symptoms required for a diagnosis of ASD are not required for a diagnosis of PTSD, although dissociative symptoms may commonly be seen in PTSD patients. Secondly, PTSD need not arise within one month of exposure to the traumatic stressor, and may emerge months or years after the traumatic event. Thirdly, in contrast to the one month maximum duration of symptoms required for a diagnosis of ASD, symptoms must persist for at least one month in order for a diagnosis of PTSD to be made.

Skilled clinicians routinely diagnose patients with PTSD based on unstructured clinical interactions. Nonetheless, several self-reported and clinician-administered rating scales may be used to diagnose PTSD and are suitable to select patients in need of anti-glucocorticoid therapy. Clinician-administered rating scales include the Structured Interview for PTSD (SI-PTSD; Davidson et al., *J Nervous Mental Disease* 177:336–41 (1989)), the Clinician Administered PTSD Scale (CAPS; Blake et al., *Behavior Therapist* 13:187–8 (1990)) and the Short Screening Scale for DSM-IV PTSD (Breslau et al., *Am J Psychiatry* 156:908–11 (1999)). Suitable self-reported rating scales include the complete and short-form Mississippi Scale for Combat-Related PTSD (Keane et al., *J Consult Clin Psychol* 56:85–90 (1988); Fontana & Rosenbeck, *J Traumatic Stress* 7:407–14 (1994)), the Revised Civilian Mississippi Scale for PTSD (Norris & Perilla, *J Traumatic Stress* 9:285–98 (1996)), and the Davidson Trauma Scale (Davidson et al., *Psychological Med* 27:153–60 (1997)). Similar to the rating scales for ASD, cutoff scores for PTSD diagnosis are determined by selecting a score that yields optimum sensitivity, specificity, positive predictive value and negative predictive value (e.g., a score of 4 or greater on the Short Screening Scale for DSM-IV PTSD; Breslau et al., supra).

3. Diagnosis of Brief Psychotic Disorder with Marked Stressor(s)

A Brief Psychotic Disorder is a short-term (between one day and one month) disturbance involving the sudden onset of at least one psychotic symptom, such as delusions, hallucinations, disorganized speech, or grossly disorganized or catatonic behavior. Brief Psychotic Disorders exclude those induced by a general medical condition. If psychotic symptoms develop shortly after, and apparently in response to, one or more severely stressful events, the disturbance is diagnosed as Brief Psychotic Disorder with Marked Stressor (s) (formerly labeled "brief reactive psychosis" in DSM-III-R). Brief Psychotic Disorder with Marked Stressor(s) is treatable by the glucocorticoid receptor antagonists of the present invention.

Brief Psychotic Disorder with Marked Stressor(s) is generally diagnosed in unstructured clinical interactions, in which skilled clinicians assess whether a patient's symptoms fall within the DSM-IV-TR criteria for the disorder. Brief Psychotic Disorder with Marked Stressor(s) may also be diagnosed with a standardized test instrument in a structured clinical interview. A suitable standardized instrument is First et al., *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition With Psychotic Screen* (*SCID-I/P W/PSY SCREEN*), New York: Biometrics Research, New York State Psychiatric Institute (1997).

4. General Laboratory Procedures

When practicing the methods of the invention, a number of general laboratory tests can be used to assist in the diagnosis, progress and prognosis of the patient with stress disorders, including monitoring of parameters such as blood cortisol, drug metabolism, brain structure and function and the like. These procedures can be helpful because all patients metabolize and react to drugs uniquely. In addition, such monitoring may be important because each GR antagonist has different pharmacokinetics. Different patients and disease conditions may require different dosage regimens and formulations. Such procedures and means to determine dosage regimens and formulations are well described in the scientific and patent literature. A few illustrative examples are set forth below.

a. Determining Blood Cortisol Levels

Varying levels of blood cortisol, especially high levels of cortisol, have been associated with stress disorders, although the invention may also be practiced upon patients with apparently normal levels of blood cortisol. See Mazure et al., *Biol Psychiatry* 41:865–70 (1997). Thus, monitoring blood cortisol and determining baseline cortisol levels are useful laboratory tests to aid in the diagnosis, treatment and prognosis of a stress disorder patient. A wide variety of laboratory tests exist that can be used to determine whether an individual is normal, hypo- or hypercortisolemic. Stress disorder patients typically have normal levels of cortisol that are often less than 25 μg/dl in the afternoon, and frequently about 15 μg/dl or less in the afternoon, although the values often fall at the high end of the normal range, which is generally considered to be 5–15 μg/dl in the afternoon.

Immunoassays such as radioimmunoassays are commonly used because they are accurate, easy to do and relatively cheap. Because levels of circulating cortisol is an indicator of adrenocortical function, a variety of stimulation and suppression tests, such as ACTH Stimulation, ACTH Reserve, dexamethasone suppression test (see, e.g., Greenwald, *Am. J. Psychiatry* 143:442–446, 1986), can also provide diagnostic, prognostic or other information to be used adjunctively in the methods of the invention.

One such assay available in kit form is the radioimmunoassay available as "Double Antibody Cortisol Kit" (Diagnostic Products Corporation, Los Angeles, Calif.), *Acta Psychiatr. Scand.* 70:239–247, 1984). This test is a competitive radioimmunoassay in which ^{125}I-labeled cortisol competes with cortisol from an clinical sample for antibody sites. In this test, due to the specificity of the antibody and lack of any significant protein effect, serum and plasma

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