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(54) **METHODS FOR TREATING PSYCHOSIS ASSOCIATED WITH COCAINE ADDICTION WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS**

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(60) Provisional application No. 60/060,973, filed on Oct. 6, 1997.

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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 ameliorating pathologies or conditions associated with psychosis. These pathologies or conditions include psychotic major depression, schizoaffective disorders, Alzheimer's Disease and cocaine addiction. Mifepristone, a potent glucocorticoid receptor antagonist, can be used in these methods. The invention also provides a kit for the amelioration of psychosis in a human including a glucocorticoid receptor antagonist and instructional material teaching the indications, dosage and schedule of administration of the glucocorticoid receptor antagonist.

12 Claims, No Drawings

METHODS FOR TREATING PSYCHOSIS ASSOCIATED WITH COCAINE ADDICTION WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of Ser. No. 09/244,457, filed Feb. 4, 1999, now U.S. Pat. No. 6,150,349, which is a continuation of PCT/US98/20906, filed Oct. 5, 1998, which is a continuation-in-part of U.S. Provisional Application Ser. No. 60/060,973, filed Oct. 6, 1997. The aforementioned application 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 its receptor can be used in methods of ameliorating psychosis, including the psychotic component of pathologies or conditions with psychotic symptoms.

INTRODUCTION

This invention is directed to a method for treating psychosis whose pathogenesis is related to glucocorticoid regulatory dysfunction. The types of psychosis treated by the methods of the invention must be distinguished from the older definition of psychosis, which referred to schizophrenia and manic states. Schizophrenia and manic states are not associated with dysfunction of the glucocorticoid regulatory pathway and there is no basis to believe that possibility. Thus, the treatment methods of the invention encompass the modem usage of the term psychosis, i.e., non-schizophrenia and non-manic state associated psychosis.

There has been historic confusion in the definition of psychosis. This is, in part, based on a lack of understanding of a common pathophysiologic mechanism causing psychosis in various conditions. For example, Oberlander, et al., WO 98/26785, teaches use of an anti-glucocorticoid to treat schizophrenia and manic states. However, schizophrenia and manic states are are believed to be the result of abnormal nerve structure, i.e., "hard-wiring" problems. In contrast, it is believed that the pathophysiology of psychosis (the term used in its modem sense, as used in the instant invention) is related to neurochemical (glucocorticoid regulatory) problems. This theory is extended by the instant invention, in which it was surprisingly discovered that agents which inhibit the binding of cortisol to its receptor can be used to treat psychosis.

Today it is known that psychotic patients can be distinguished from other psychiatric problems in that they have a glucocorticoid regulatory dysfunction. In contrast, patients with schizophrenia and manic states do not have glucocorticoid regulatory dysfunction (see, e.g., Rothschild (1982) *Br. J. Psychiatry* 141:471–474; Clower (1986) *J. Clin. Psychopharmacol.* 6:363–365). Thus, schizophrenia and manic states are not within the scope of the definition of "psychosis" (as defined either by the medical profession, or, as used herein), and thus are not treated by the methods of the invention.

In most species, including man, the physiological glucocorticoid is cortisol (hydrocortisone). Glucocorticoids are secreted in response to ACTH (corticotropin), which shows both circadian rhythm variation and elevations in response

to stress and food. Cortisol levels are responsive within minutes to many physical and psychological stresses, including trauma, surgery, exercise, anxiety and depression. Cortisol is a steroid and 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 which 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 those caused by hypercortisolemia, can be modulated at the GR level using receptor antagonists. Several different classes of agents are able to block the physiologic effects of GR-agonist binding. 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 such known GR antagonist, mifepristone, has been found to be an effective anti-glucocorticoid agent in humans (Bertagna (1984) *J. Clin. Endocrinol. Metab.* 59:25). Mifepristone binds to the GR with high affinity, with a K of dissociation $\leqq 10^{-9}$ M (Cadepond (1997) *Annu. Rev. Med.* 48:129).

Patients with some forms of psychiatric illnesses have been found to have increased levels of cortisol (Krishnan (1992) *Prog. Neuro-Psychopharrnacol. & Biol. Psychiat.* 16:913–920). For example, some patients with depressed mood have had their mood improve with treatments which lower the levels of cortisol. In some individuals, reversing increased cortisol levels using inhibitors of steroid biosynthesis can be effective in treating depression (Murphy (1991) *J. Steroid Biochem. Mol. Biol.* 39:239; Murphy (1991) *J. Clin. Psychopharmcol.* 11:121; Dhar (1989) *Clin. Invest. Med.* 12:B27). Alternatively, some depressed individuals can be responsive to treatments which block the effect of cortisol, as by administering GR antagonists (Van Look (1995) *Human Reproduction Update* 1:19–34). In one study, a patient with depression secondary to Cushing's Syndrome (hyperadrenocorticism) was responsive to a high dose, up to 1400 mg per day, of GR antagonist mifepristone (Nieman (1985) *J. Clin Endocrinol. Metab.* 61:536). Another study which used mifepristone to treat Cushing's syndrome found that it improved the patients' conditions, including their psychiatric status (Chrousos, pp 273–284, In: Baulieu, ed. The Antiprogestin Steroid RU 486 and Human Fertility Control. Plenum Press, New York (1989), Sartor (1996) *Clin. Obstetrics and Gynecol.* 39:506–510). Mifepristone has been used to treat major depression. Using from about 2.5 to 4.4 mg/kg per day for periods up to eight weeks, one group found that four patients with chronic severe depression, who were resistant to conventional therapies, responded to treatment (Murphy (1993) *J. Psychiatr. Neurosci.* 18:209).

Psychosis has also been associated with Cushing's syndrome (Gerson (1985) *Can. J. Psychiatry* 30:223–224; Saad (1984) *Am. J. Med.* 76:759–766). Mifepristone has been used to treat acute psychiatric disturbances secondary to Cushing's syndrome. One study showed that a relatively high dose of mifepristone (400 to 800 mg per day) was useful in rapidly reversing acute psychosis in patients with severe Cushing Syndrome due to adrenal cancers and ectopic secretion of ACTH from lung cancer (Van der Lely (1991) *Ann. Intern. Med.* 114:143; Van der Lely (1993) *Pharmacy World & Science* 15:89–90; Sartor (1996) supra).

Psychotic major depression has long been recognized as a distinct psychiatric illness, having both psychotic and depressive components. In a differential diagnosis, it is important that psychotic major depression be distinguished

from nonpsychotic major depression, because effective treatments and patterns of response to pharmacologic therapies for psychotic major depression are very different from those relating to non-psychotic major depression. Successful treatment depends on the accuracy of the initial diagnosis. (Glassman (1981) *Arch. Gen. Psychiatry* 38:424–427, Schatzberg (1992) *Am. J. Psychiatr.* 149:733–745, Schatzberg (1988) *Annals N.Y. Acad. of Sci.*537:462). Psychotic major depression is very common. It has been estimated that twenty five percent of depressed patients admitted to the hospital have psychotic major depression (Coryell (1984) *J. Nerv. Ment. Dis.* 172:521).

Before this invention, there was to fast-acting effective treatment without significant side effects for the treatment of psychosis or the psychotic component of illnesses and conditions associated with psychosis, such as psychotic major depression. Individuals suffering from psychotic major depression have a low placebo response rate and respond poorly to antidepressant therapy alone, i.e., without concurrent treatment with antipsychotic medication (Glassman (1975) *Am. J. Psychiatry* 132:716–719; Avery (1979) *Am. J. Psychiatry* 135:559–562). While psychotic depression can respond to electroconvulsive therapy (ECT), this form of treatment is controversial, can have significant side effects, has a relatively slow response rate and has a high level of related morbidity. Similarly, another commonly used treatment for psychotic major depression, a combination therapy of currently available antipsychotic and antidepressant medications, has a slow onset of action and a relatively high rate of morbidity (Minter (1979) *J. Nerv. Ment. Dis.* 167:726–733).

Thus, there exists a great need for a more effective and safer treatment for psychosis and illnesses and conditions associated with psychosis, including psychotic major depression. There is a great need for a new treatment for psychotic major depression which has a quick response time, has few side effects, decreases the amount of time a patient must be institutionalized and has a lower rate of morbidity. Furthermore, there exists a variety of conditions which have a psychotic element for which there is no known cure or effective treatment. These include schizoaffective disorder, Alzheimer's Disease and cocaine addiction. Thus, there exists a great need for a safe and effective treatment for these conditions. The present invention fulfills these and other needs.

SUMMARY OF THE INVENTION

The invention is directed to a method of treating psychosis associated with glucocorticoid related dysfunction by administration of an amount of a glucocorticoid receptor antagonist effective to ameliorate the psychosis, with the proviso that the patient not be suffering from Cushing's Syndrome. In alternative embodiments of this method, the psychosis is associated with psychotic major depression, schizoaffective disorder, Alzheimer's Disease and cocaine addiction.

In further embodiments, the glucocorticoid receptor antagonist used in the methods can comprise 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 of the invention, the glucocorticoid receptor antagonist can comprise mifepristone (RU486), RU009 or RU044. The glucocorticoid receptor antagonist can be administered in a daily amount of between about 8 to 20 mg per kilogram of body weight per day, or, in a daily amount of about 8 to 12 mg per kilogram of body weight per day. The glucocorticoid receptor antagonist can be administered for about four days. It can be administered in a daily amount of about 600 mg per day. The administration can be once per day. Its mode of administration can be oral or transdermal.

In a preferred embodiment, the invention relates to a method of ameliorating psychotic depression comprising administering a mifepristone in a daily amount of about 8 to 12 mg per kilogram of body weight per day, wherein the administration continues for a period of about four days.

The invention also relates to a kit for the amelioration of psychosis 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. The kit's instructional material can indicate that the glucocorticoid receptor antagonist can be administered in a daily amount of about 8 to 12 mg per kilogram of body weight per day. The instructional material can indicate that the administration of the glucocorticoid receptor antagonist can continue for a period of about four days.

In one embodiment, the kit is for the amelioration of psychosis as a component of psychotic major depression and the instructional material indicates that the glucocorticoid receptor antagonist can be used for the treatment of psychotic major depression. In a preferred embodiment, the kit's glucocorticoid receptor antagonist is mifepristone, which can be in tablet form.

The invention also relates to a novel means of diagnosing and assessing treatments for psychosis using color-word recognition tests. In one embodiment, the Stroop Color and Word Test, or variations thereof, is used to objectively determine whether an individual is psychotic, the degree of psychosis and the efficacy of an antipsychotic treatment regimen. The invention also provides a color-word test to differentially diagnose psychotic major depression from non-psychotic major depression.

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

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

DEFINITIONS

The term "ameliorating" or "ameliorate" refers to any indicia of success in the treatment of a pathology or condition, including any objective or subjective parameter such as abatement, remission or diminishing of symptoms or an improvement in a patient's physical or mental well-being. Amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination and/or a psychiatric evaluation. For example, a clinical guide to monitor the effective amelioration of a psychiatric disorder, such as psychosis or depression, is found in the Structured Clinical Interview for DSM-IV Axis I mood disorders ("SCID-P") (see fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (1994) Task Force on DSM-IV, American Psychiatric Association ("DSM-IV"); Kaplan, Ed. (1995) *Comprehensive Textbook of Psychiatry/VI*, vol. 1, sixth ed., pp 621–627, Williams & Wilkins, Balt., Md.).

The term "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 "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.

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

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 glucocorticoid receptor, typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a 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-1)-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-dimethylaino)phenyl]-17A-(prop-1-ynyl)-D-4,9-estradiene-17B-ol-3-one.

The term "psychotic" as used herein refers to a psychiatric condition in its broadest sense, as defined in the DSM-WV (Kaplan, ed. (1995) supra) and described below. The term "psychotic" has historically received a number of different definitions, ranging from narrow to broadly described. A psychotic condition can include delusions or prominent hallucinations, including prominent hallucinations that the individual realizes are hallucinatory experiences, and those with hallucinations occurring in the absence of insight into their pathological nature. Finally, the term includes a psychotic condition characterized by a loss of ego boundaries or a gross impairment in reality testing. Unlike this definition, which is broad and based primarily on symptoms, characterization of psychosis in earlier classifications (e.g., DSM-II and ICD-9) were more inclusive and focused on the severity of functional impairment (so that a mental disorder was termed "psychotic" if it resulted in "impairment" that grossly interferes with the capacity to meet ordinary demands of life). Different disorders which have a psychotic component comprise different aspects of this definition of "psychotic." For example, in schizophreniform disorder, schizoaffective disorder and brief psychotic disorder, the term "psychotic" refers to delusions, any prominent hallucinations, disorganized speech, or disorganized or catatonic behavior. In psychotic disorder due to a general medical condition and in substance-induced psychotic disorder, "psychotic" refers to delusions or only those hallucinations that are not accompanied by insight. Finally, in delusional disorder and shared psychotic disorder, "psychotic" is equivalent to "delusional" (see DSM-IV, supra, page 273).

Objective tests can be also be used to determine whether an individual is psychotic and to measure and assess the success of a particular treatment schedule or regimen. For example, measuring changes in cognitive ability aids in the diagnosis and treatment assessment of the psychotic patient. Any test known in the art can be used, such as the so-called "Wallach Test," which assesses recognition memory (see below, Wallach (1980) *J. Gerontol.* 35:371–375). For example, as described in Example 1, when the Wallach Recognition Test was used to measure the degree of amelioration of psychosis in the study's subjects, on the average, test subjects identified fewer distracters over words they had actually heard before. The number of distracting words mis-identified as words actually presented in the test declined between 25% and 100% after treatment. Another example of an objective text which can be used to determine whether an individual is psychotic and to measure efficacy of an anti-psychotic treatment is the Stroop Color and Word Test ("Stroop Test") (see Golden, C. J., Cat. No. 30150M, In *A Manualfor Clinical and Experimental Uses, Stoelting*, Wood Dale, Ill.). The Stroop Test is an objective neuropsychiatric test that can differentiate between individuals with psychosis and those without, and is described in detail below.

The term "psychosis" refers to a psychiatric symptom, condition or syndrome in its broadest sense, as defined in the DSM-IV (Kaplan, ed. (1995) supra), comprising a "psychotic" component, as broadly defined above. The term psychosis can refer to a symptom associated with a general medical condition, a disease state or other condition, such as a side effect of drug abuse (a substance-induced disorder) or as a side effect of a medication. Alternatively, the term psychosis can refer to a condition or syndrome not associated with any disease state, medical condition, drug intake or the like. Psychosis is typically defined as a mental disorder or condition causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with his capacity to cope with the ordinary demands of everyday life.

Historically, the term "psychosis" was sometimes used to describe schizophrenia and manic states (these conditions are separately described in the DSM-IV, supra). However, the current medical view, as embraced by the DSM-IV, supra, does not include these psychiatric conditions as including psychosis. There is a physiologic basis for this discrimination, which was recognized as early as Rothschild, et al. (1982) "The dexamethasone suppression test as a discriminator among subtypes of psychotic patients," *Br. J. Psychiatry* 141:471–474; and, Clower (1986) "The 2-mg dexamethasone suppression test in differentiating major depression with psychosis from schizophrenia," *J. Clin. Psychopharmacol.* 6:363–365. The dexamethasone suppression (DS) test indicates a dysfunction in the glucocorticoid regulatory feedback pathway, which is controlled by the hypothalamic-pituitary-adrenal (HPA) axis (non-responsiveness in the test means a patient cannot suppress (negatively feedback) cortisol production when challenged with a test dose of a synthetic glucocorticoid, dexamethasone). Most psychotic patients have a glucocorticoid regulatory dysfunction (as indicated by non-responsiveness in the DS test). In contrast, patients with, e.g., schizophrenia (including those historically described as "psychotic schizophrenics") and manic states, do not have glucocorticoid regulatory dysfunction (as indicated by responsiveness in the DS test). It is widely believed that schizophrenia and manic states are caused by abnormal nerve structure, i.e., a "hard-wiring" problem. In contrast, it is believed that the pathophysiology of psychosis is related

to neurochemical problems, particularly, HPA axis regulatory dysfunction (this theory is extended by the instant invention, in which it was discovered that that agents which inhibit the binding of cortisol to its receptor will treat psychosis). Thus, schizophrenia and manic states are not within the scope of the definition of "psychosis" (as defined either by the medical profession, or, as used herein), and thus are not treated by the methods of the invention.

The term "psychotic major depression," also referred to as "psychotic depression" (Schatzberg (1992) *Am. J. Psychiatry* 149:733–745), "psychotic (delusional) depression" (Ibid.), "delusional depression" (Glassman (1981) supra) and, "major depression with psychotic features" (see the DSM-III-R), refers to a distinct psychiatric disorder which includes both depressive and psychotic features. Individuals manifesting both depression and psychosis, i.e. psychotic depression, are herein referred to as "psychotic depressives." It has been long-recognized in the art as a distinct syndrome, as described, for example, by Schatzberg (1992) supra. Illustrative of this distinctness are studies which have found significant differences between patients with psychotic and nonpsychotic depression in glucocorticoid activity, dopamine-beta-hydroxylase activity, levels of dopamine and serotonin-metabolites, sleep measures and ventricle to brain ratios. Psychotic depressives respond very differently to treatment compared to individuals with other forms of depression, such as "non-psychotic major depression." Psychotic depressives have a low placebo response rate and a respond poorly to antidepressant therapy alone (without concurrent anti-psychotic treatment). Psychotic depressives are markedly unresponsive to tricyclic (anti-depressive) drug therapy (Glassman, et al. (1975) supra). While psychotic depressives can respond to electroconvulsive therapy (ECT), their response time is relatively slow and the ECT has a high level of related morbidity. Clinical manifestations and diagnostic parameters of "psychotic major depression" is described in detail in the DSM-IV (Kaplan, ed. (1995) supra). Thus, due to its unique pathophysiology, high rate of morbidity and response to treatment, there is great practical need to differentially diagnose and specifically treat psychotic major depression as compared to non-psychotic depression.

DETAILED DESCRIPTION OF THE INVENTION

This invention pertains to the discovery that agents that can inhibit a biological response caused by an agonist-occupied glucocorticoid receptor (GR) are effective for ameliorating the mental disorder, or syndrome, of psychosis. Because the condition of psychosis can be associated with or caused by a variety of conditions and disease processes, the methods of the invention also are used to ameliorate the psychotic component of pathologies or conditions involving psychosis. These pathologies or conditions include psychotic major depression, schizoaffective disorders, Alzheimer's Disease, cocaine addiction, drug side effects and the like.

In one embodiment, the methods of the invention use agents that act as GR antagonists, blocking the interaction of cortisol with GR, thereby ameliorating psychosis. In another embodiment, mifepristone, a potent GR antagonist, is used in methods to ameliorate psychosis. The invention provides a new, effective treatment for psychotic major depression which is relatively fast, has fewer side effects, decreases the amount of time a patient must be institutionalized and has a lower rate of morbidity when compared to alternative treatments.

As psychosis can be manifested as a mental illness in the form of a syndrome or as an element of a disease process or other condition, various means of diagnosing and assessing the success of treatment, i.e., the success and extent the psychosis is ameliorated, are set forth below. These means include classical psychological evaluations and various laboratory procedures. As the methods of the invention include use of any means to inhibit the biological effect of a GR to ameliorate psychosis, illustrative compounds and compositions which can be used to treat psychosis 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. General Laboratory Procedures

A number of general laboratory tests can be used to assist in the diagnosis, progress and prognosis of the patient. Monitoring of parameters such as blood cortisol, drug metabolism, brain function and the like may be needed because all patients metabolize and react to drugs uniquely. In addition, such monitoring may be important because each GR antagonist has different pharmnacokinetics. Different disease conditions may require different dosage regimens and formulations. Such procedures are well described in the scientific and patent literature. A few illustrative examples are set forth below.

a. Determining Blood Cortisol Levels

Because levels of blood cortisol have been associated with psychosis and depression, monitoring blood cortisol levels can be a useful laboratory test to aid in the diagnosis, treatment and prognosis of the patient. A wide variety of laboratory tests exist that can be used to determine whether an individual is normal, hypo- or hypercortisolemic. 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 adrenocorticol function, a variety of stimulation and suppression tests, such as ACTH Stimulation, ACTH Reserve, Dexamethasone Suppression, 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 radioinimunoassay available as "Double Antibody Cortisol Kit™" (Diagnostic Products Corporation, Los Angeles, Cali., (1984) *Acta Psychiatr. Scand.* 70:239–247). 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 samples require neither preextraction nor predilution. This assay is described in further detail in Example 1, below.

i. Determining Blood/Urine Mifepristone Levels

Because a patient's metabolism, clearance rate, toxicity levels, etc. differs with variations in underlying primary or secondary disease conditions, drug history, age, general medical condition and the like, it may be necessary to measure blood and urine levels of GR antagonist. Means for such monitoring are well described in the scientific and patent literature. As in one embodiment of the invention mifepristone is administered to ameliorate psychosis, an illustrative example of determining blood and urine mifepristone levels is set forth below.

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