

Review article

**The role of glucocorticoids in mood symptoms modulation: a review**

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## INTRODUCTION

The major function of the adrenal cortex consists of secreting glucocorticoids and mineralocorticoids hormones, of which cortisol and aldosterone are the most important in the human being organism as they regulate, respectively, carbohydrates and hemodynamic functions. Those hormones are essential to life, especially in response to stressful situations.<sup>1</sup> The adrenal cortex consists of almost 90% of the adrenal gland, covering the gland medulla. It is responsible for the production of catecholamines and it can be divided into three distinct layers of tissue: *zona glomerulosa*, which produces aldosterone; *zona reticularis* and *zona fasciculata*, which are 75% of the gland and produce cortisol and androgens.<sup>1</sup>

The hypothalamic-pituitary-adrenal (HPA) axis corresponds to a regulatory system that integrates endocrine and neurological functions. The neurosecretory cells of the hypothalamic paraventricular nucleus (PVN) secrete the corticotropin-releasing hormone (CRH) and the arginine vasopressin (AVP) in the hypophyseal portal circulation. In the adenohypophysis, or anterior pituitary, they stimulate the release of the adrenocorticotrophic hormone (ACTH), which promotes the release of cortisol in the adrenal cortex. Cortisol is the final product of HPA and it has central and peripheral functions mediated through at least two types of specific receptors: type 1 or mineralocorticoid receptor (MR) of high affinity, firstly described by McEwen et al.,<sup>2</sup> and type 2 or glucocorticoid receptor (GR) of low affinity. Type 1 receptors exhibit high affinity for corticosterone in rats and are found in large concentrations in extra-hypothalamic limbic neurons of the hippocampus-septal region, while they are not so concentrated in the hypophysis. They also have high affinity with aldosterone and therefore were named mineralocorticoid receptors by Beaumont & Fanestil.<sup>3</sup> Type 2 receptors exhibit high affinity with synthetic glucocorticoids as dexamethasone and RU28362, and low affinity with endogenous glucocorticoids (EG).<sup>4,5</sup>

## METHOD

MEDLINE and BIREME were searched for the keywords cortisol, corticosteroids, depression, bipolar disorder and psychosis in English, French, and Spanish from 1993 to 2003. Original (35) and review (22) articles were included; case reports were not included in the study.

### *Regulation of the HPA axis*

According to McQuade & Young<sup>6</sup> and Muller et al.,<sup>7</sup> nearly all neurotransmitters affect the secretion of CRH, which is a potent stimulus for ACTH secretion. The AVP stimulation is not so intense, but it markedly potentiates the effects of CRH. The secretory cells in the PVN receive neuronal inputs from many brain regions, and monoamines, as serotonin (5HT), noradrenaline (NA), acetylcholine (Ach) and both excitatory and inhibitory amino acids are involved in the regulatory CRH secretion.<sup>6</sup> In addition to these extrinsic regulatory inputs to the HPA axis, an intrinsic autoregulatory mechanism also exists: the endogenous cortisol acts as a potent negative regulator of the HPA activity by binding to glucocorticoid receptors in the HPA axis tissues and the hippocampus.<sup>6</sup> The MR and the GR actions are yet unclear, however, MRs receptors are likely to control low basal levels of cortisol, while GR receptors come into play during the circadian and stress-related peaks in cortisol.<sup>6</sup>

### *Steroids basic mechanisms of action*

Cowen<sup>8</sup> points out that corticosteroids can affect brain functions in two ways: interacting with the genome or with the cell membranes. Corticosteroids freely penetrate the cell membrane. In neurons that have steroid-specific receptors in the cytoplasm of cells, the steroid-receptor complex (SRC) penetrates the cellular nucleus. The SRC binds to chromatin and regulates the transcription of specific genes. Those molecular events may contribute to the understanding of the steroids effect over behavior, once neurons contain steroid-specific receptors concentrated in the hippocampus,

septum and amygdalae, which are brain parts intimately involved in the human behavior, mood, learning and memory abilities.<sup>8</sup>

Molecular events include alteration of levels of enzymes, such as tyrosine hydroxylase, tryptophan hydroxylase, monoamine oxidase, dopamine beta-hydroxylase and phenylethanolamine-N-methyltransferase, which control the activity of amines and alteration of levels of mRNA coding, such as somatostatin, CRH, ACTH, beta-endorphin and G-proteins.<sup>9</sup> Steroids also affect the pre and post synaptic activities, by modifying the concentrations of serotonergic 5HT<sub>1A</sub> and alpha-2 and beta-e adrenergic receptors.<sup>9</sup> Yet, according to Cowen<sup>8</sup> some of these actions can neutralize the effects of antidepressant drugs in beta-adrenergic receptors. On the other hand, it is not known how corticosteroids affect serotonergic receptors, for the few works developed so far present contradictory results.<sup>10</sup>

The effects of corticosteroids in 5HT receptors can play an important role in the vegetative and affective functions. In experiments with laboratory animals,<sup>11</sup> chronically stressed rats were shown to have increased corticosterone secretion, decreased 5HT<sub>1A</sub> mRNA levels and increased depressive behavior, such as less locomotion, decreased open-field behavior and anorexia. However, after 5 to 7 days of continuous stress exposure, the activity of 5HT<sub>1A</sub> receptors normalize, as well as animals behavior. These adaptive responses in 5HT<sub>1A</sub> activity and behavior were curtailed by repeated administration of corticosterone, but were facilitated by antigluccorticoid drug administration.<sup>11</sup> These findings suggest that there may be antidepressant effects of antigluccorticoid drugs.<sup>9</sup>

In addition to genomically mediated effects, there are interaction mechanisms with cell membranes that change the ion conductance and the interaction with membrane receptors, as the GABA receptors.<sup>9</sup>

### *Glucocorticoid-mediated response to stress*

The main endocrine response to stress seen in human beings and animals is the activation of the HPA axis.<sup>12</sup> Results of such stimulation are essential for survival, once adrenalectomized animals exposed to stressors to which they would normally survive can have a fatal end.<sup>13</sup>

Sapolsky et al.<sup>14</sup> divide the stress response in two waves: the first wave happens soon after the stressful situation, it enhances the secretion of catecholamines (epinephrin and norepinephrin) from the sympathetic nervous system; the release of CRH into the portal circulation and perhaps 10 seconds later, enhanced secretion of ACTH. Besides, there is decreased release of GnRH (gonadotrophin releasing hormone) and, thereafter decreased secretion of pituitary gonadotrophins and of GH (growing hormone), as well as pancreatic secretion of glucagon. In the case of a hemorrhage, this first wave also includes massive secretion of AVP from the pituitary and renin from the kidney.

The second wave involves the steroid hormones: over the course of minutes, GC secretion is stimulated and gonadal steroid secretion declines.<sup>14</sup>

According to Sapolsky et al.,<sup>14</sup> the glucocorticoid actions are also divided in **modulating** actions (permissive, suppressive and stimulatory) and **preparative** actions. The **permissive** actions are exerted by GCs present before the stressor and prime the defense mechanisms by which an organism responds to stress. Their consequences are first manifested during the initial stress response and occur whether or not there is a stress-induced increase in GC concentrations; the **suppressive** actions are those attributable to the stress-induced rise in GC concentrations, and thus have an onset of from about an hour or more after the onset of the stressor. These relatively delayed GC actions rein in the stress-activated defense reactions and prevent them from overshooting; the **stimulating** actions are also attributable to the stress-induced rise in GC concentrations. They enhance the first wave of hormonal responses to stress and thus are the reverse of the suppressive actions. Eventually, **preparative** actions are defined as those that do not affect the immediate response to a stressor, but modulate the organism's response to a subsequent stressor.<sup>14</sup>

Even though high levels of GC are essential in an acute response to stress, chronically high levels of stress may have significant negative effects in brain functions activity.<sup>13</sup>

#### *HPA axis dysfunctions and psychiatric symptoms*

In the late 1950s, Board observed that the basal level of plasma cortisol in patients with depression was higher than in healthy controls.<sup>15</sup> Gibbons<sup>16</sup> corroborated this finding and added that the plasma levels of cortisol during remission of a depressive event were smaller during the acute phase of the disease. There are studies on the HPA axis activities in patients with depression that evidenced an enhanced cortisol response to ACTH stimulation; decreased cortisol response to hypoglycemia; decreased ACTH response to stimulation with CRH; and resistance to cortisol suppression by dexamethasone (in the test of dexamethasone suppression), which suggested a possible relation between suppression and depression severity.<sup>17</sup>

Murphy,<sup>17</sup> Musselman & Nemeroff<sup>18</sup> and Zobel et al.<sup>19</sup> showed that large concentrations of CRH and AVP in the cerebrospinal fluid (CSF), not only stimulate the ACTH and corticosteroids secretion, but also cause behavioral and autonomic changes associated to depression. Moreover, according to Zobel et al.,<sup>19</sup> there is a relation between hypercortisolemia and enhanced concentration of CRH in the CSF in patients with depression, suggesting that the negative feedback of the endogenous cortisol is not regulated.

According to Murphy<sup>17</sup> the dexamethasone suppression test (DST) measures the functional integrity of the negative feedback mechanism mediated by GR, thereby the suppressive activity of the synthetic cortisol release (dexamethasone) works as an indicator of GR activity. The fact that the cortisol release is not suppressed after the DST in patients with depression and bipolar disorder suggests an abnormal behavior of GR in those diseases.<sup>17</sup> Yehuda et al.<sup>20</sup> consider that it seems to have a decrease in the number of GR in patients with depression and an increase of this number in patients with post-traumatic distress syndrome as compared to patients with bipolar and panic disorders and with schizophrenia. Besides, there is an unbalance between GR and the MR in

patients with depression, this means, there is a decrease in the activity of GR and an increase in the activities of MR.<sup>21</sup> Alvarez et al.<sup>22</sup> found an abnormal response to the DST in patients with major depression as compared to schizophrenic patients and healthy controls. For Stefos<sup>23</sup> and Nelson & Davis<sup>24</sup> the psychotic depression is the sub-type most associated to hypercortisolemia and non-cortisol suppression after DST. Van Wijnendaele et al.<sup>25</sup> found abnormal results in DST in about 50% from the 130 patients studied for biological abnormalities in depressant patients.

The DST methodology has been criticized for not taking into account the regulator role of CRH, and those changes resulted in a combined test of dexamethasone with CRH (DEX/CRH),<sup>6</sup> which according to Holsboer et al.<sup>26</sup> is the best instrument available for the identification of abnormalities in the HPA axis in psychiatric patients. The cortisol response to the combined test can be a medium term prognosis after a depressive event: non suppression after the combined test reflects a higher risk of relapse for patients in a period of six months, as compared to those with a low response.<sup>19</sup> Healthy patients with significant familial history of depression presented abnormal findings for the combined test DEX/CRH (results among patients with depression and controls) and have presented the same results for up to four years. According to Modell et al.,<sup>27</sup> this fact suggests a relationship between the abnormal findings of the test and depression vulnerability.<sup>27, 28</sup>

Besides, those tests normalize after mood symptoms remission, suggesting that the normal functions of GR are related to the mechanism of action of drugs used in mood disorders treatment.<sup>10,26</sup> According to Wolkowitz & Reus,<sup>9</sup> the hypercortisolemia (basally or in response to the DST) is evident in patients with major depression and has been correlated with different behavioral alterations such as: sleep disturbance, decreased energy, decreased attention and libido, psychomotor disturbance, anxiety and suicidal ideation. Of note, according to Wolkowitz & Reus<sup>9</sup> other difficulties with interpreting those data include the facts that not all depressed patients are hypercortisolemic and that not all hypercortisolemic individuals are depressed. The glucocorticoids and the CRH may interact and magnify such symptoms as fear, anguish and anticipation of

adversity. It is plausible that multiple hormonal aberrations contribute to the final clinical presentation in major depression.<sup>9</sup>

Cassidy et al.<sup>29</sup> pointed out that Dexamethasone levels were lower and cortisol levels higher in those patients diagnosed mixed bipolar disorder, as compared to those with manic bipolar disorder.

Dysthymic patients have been reported to have a good response to fluoxetine and had higher concentration of cortisol after DST as compared to those who did not present the same response, however these findings do not prove that hypercortisolemia is an indicator of a good response of dysthymic patients to antidepressants.<sup>30</sup>

There is also evidence of an association between high concentrations of cortisol and specific cognitive deficit, such as decrease of verbal memory.<sup>31,32</sup> Neylan et al.<sup>32</sup> point out that high plasma concentrations of corticosteroids increase the vulnerability of the brain to the adverse effects of repeated seizures, so that cognitive impairment increases in depressed patients who receive electroconvulsive therapy (ECT) for major depression. Joyce et al.<sup>33</sup> have reported that cortisol levels are higher in patients with depression as compared to healthy controls, as well as in patients with depression and melancholia, as compared to those with no melancholia symptoms. No association between hypercortisolemia and personality traits of reward dependence was found in this study. Such an association has to do with dysphoric symptoms, which means that the hypersecretion of cortisol in depressive patients depends more on the patient's clinical status than on the patient's personality traits.<sup>33</sup>

On the other hand, Strickland et al.<sup>34</sup> have shown that some female patients with depression really hypersecrete cortisol. Nevertheless, according to this study, enhanced levels of cortisol after stressors are not necessarily associated to the development of a major depressive event, and depressive events in the community are not associated to the enhancement of cortisol concentrations.<sup>34</sup> Another interesting finding in this study<sup>34</sup> was the fact that depressive women



present an elevated response of prolactin to dexfenfluramine, suggesting an increase instead of decrease of the neuroendocrine activity.

The response of prolactin to dexfenfluramine is measured by the 5HT<sub>2c</sub> receptors, which suggests an enhancement of the serotonin activity by means of those receptors. This fact can be explained by the low concentrations of tryptophan that are found in patients with depression, which decrease the available amount of serotonin, causing an adaptive response of 5HT<sub>2c</sub> receptors (upregulation).<sup>8</sup>

No associations between stressors and increased levels of salivary cortisol were found in a study by Harris et al.,<sup>35</sup> therefore, increased pre-morbid levels of cortisol and stressors are independent risk factors for the development of major depression.

Another study, by Goodyear et al.,<sup>31</sup> carried out with adolescents, evidenced that morning cortisol concentration peaks indicate a high risk of depression, as well as concentration peaks of afternoon dehydroepiandrosterone. However, no associations between the peaks of concentration of these hormones and stressors were found, suggesting what has already been reported in other studies: that these factors have an independent action.

Sapolsky<sup>36</sup> considers that besides the hormonal dysfunctions of the HPA, prolonged exposure to stress or glucocorticoids can cause brain morphological changes. Cushing's syndrome, severe and prolonged depressive episode and post-traumatic stress disorder after combat trauma can be associated to morphological changes in the CNS, such as hippocampal neuronal atrophy.<sup>36,37</sup>

The secretion of glucocorticoids as a response to stress, and their occasional deregulation during depressive episodes, have an important effect on the hippocampal neuronal plasticity, which suggests that increased levels of corticosterone concentration (main stress hormone in rodents) decrease the brain connectivity.<sup>38</sup> The possibility of decreasing volume and the fact that the activity of those neurons are associated to depression has been supported by studies that use imaging showing the brain structures atrophy.<sup>39</sup> Christensen et al.<sup>40</sup> concluded that alterations in the HPA-axis are common in patients with mood disorders, however, it is not clear whether alterations are

associated only to the acute episode or only to the disorder itself. According to Bhagwagar et al.,<sup>41</sup> HPA-axis dysfunctions with high serum cortisol concentrations seem to be typical of acute cases of major depression. This is not clear, however, because alterations are present in patients with total remission of symptoms, once salivary cortisol is shown to have high concentrations in those patients.

*Psychiatric symptoms during treatment with glucocorticoids:*

Over the last 50 years, the corticoid therapy has been widely used and prescribed in a number of systemic diseases.<sup>42,43</sup> Different from alterations secondary to hypersecretion of endogenous corticosteroids, in which depression is more common, the administration of glucocorticoids to patients with normal adrenal function usually causes mild mood disturbances, and sometimes euphoria, irritability, motor activity increase, insomnia and even psychosis, in a lower percentage.<sup>17,44</sup>

Brow et al.,<sup>37</sup> Patten & Neutel,<sup>42</sup> Sirois<sup>43</sup> and Wada et al.<sup>44</sup> consider symptoms as mania, depression and psychosis (hallucinations and deliriums) are associated to corticoid therapy, while a prolonged administration of corticoids would be more associated to depressive symptoms, and the an acute administration to mania symptoms.<sup>45</sup>

Psychiatric symptoms usually occur within the first two weeks of corticosteroid therapy, and they include mania, depression, affective lability and psychosis. Yet, symptoms may arise up to the 20th week, and are rarely seen after this period.<sup>44,46</sup> The intensity of symptoms and their longitudinal course are directly proportional to dosage. Three studies have not found symptoms with low doses of corticosteroids.<sup>44,46,47</sup> According to Rouchel et al.,<sup>48</sup> less than 2% of patients receiving prednisone (less than 40 mg/day) had psychiatric symptoms, as compared to the 4 to 6% who were receiving from 41 to 80 mg/day, and the 18.4% who received more than 80 mg/day. Potential individual risks such as presence of systemic diseases, previous history of psychiatric disease or previous use of corticosteroids still require further studies; therefore glucocorticoid drugs to patients with previous history of psychiatric diseases should be prescribed with caution.<sup>42,46,47</sup>

According to Chau & Mok,<sup>49</sup> hypoalbuminemia seems to be an indicator of enhanced probability of psychotic symptoms in patients with systemic lupus erythematosus who take glucocorticoid drugs.

Cognitive symptoms caused by corticoid prolonged administration include severe deficit with delirium, but the most frequent symptoms are mnemonic disorders mediated via the hippocampus and produced by glucocorticoids.<sup>37,50</sup> Alterations and cognitive deficits are usually reversed with treatment discontinuation.<sup>37</sup>

Withdrawal symptoms have been reported basically in long term treatments. The syndrome of glucocorticoid abstinence is characterized by tiredness, anorexia, depression, mania, delirium and depersonalization.<sup>43</sup> There are reports of psychiatric disorders when the administration of glucocorticoid drugs is changed from systemic to inhaled.<sup>37</sup> Psychiatric symptoms usually improve or remit if medication is continued, moreover, the use of tricyclic antidepressants seems to reduce tiredness and depression during the discontinuation of glucocorticoids.<sup>37</sup> Two studies with animals<sup>6,37</sup> showed that tricyclic antidepressants are able to increase the mRNA production of glucocorticoid receptors.

Psychiatric symptoms caused by glucocorticoid drugs must be initially approached by reducing or discontinuing medication.<sup>45</sup> Therefore this must be the first strategy selected.<sup>37</sup> In the case of patients who need chronic corticoid treatment, pharmacologic options should be considered: lithium is used for psychotic symptoms prophylaxis, as well as for psychotic patients treatment.<sup>44,45</sup> The disadvantages rely on the fact that several illnesses managed with corticoids, as nephrotic syndromes and lupus, cause renal dysfunction which, besides affecting the sodium balance caused by corticoids, can increase the chances of lithium intoxication.<sup>43,44</sup>

Valproic acid, lamotrigine, gabapentin, first and second generation antipsychotic medications and carbamazepine are also employed in psychiatric symptoms treatment. Carbamazepine, however, decreases the plasma concentrations of prednisolone.<sup>47</sup>

Nevertheless being useful in the treatment of psychiatric symptoms caused by the syndrome of glucocorticoids withdrawal, the Tricyclic antidepressants are associated with worsening of

agitation and psychosis. Their response in depressant patients using corticoids is also weak.<sup>37</sup>

Serotonin reuptake inhibitors have shown to be effective in the treatment of corticoid induced depression.<sup>43</sup> Low-dose olanzapine (2.5 mg/day) was also reported for severe mood swings and suicidal ideation in a patient with asthma on chronic prednisolone therapy.<sup>37</sup> Even though the use of olanzapine and risperidone have been reported, it seems to be limited to sub-acute cases.<sup>43</sup>

Haloperidol remains as the most common neuroleptic drug used to control corticoid-induced reactions. It has a versatile administration (oral, IM, IV), which facilitates the adjustment to acute and sub-acute clinic conditions.<sup>43</sup> Corticosteroid-induced psychotic disorders respond well to low doses of haloperidol,<sup>44</sup> but it poses some disadvantages, as dystonic reactions and tardive dyskinesia, when compared to second generation antipsychotics.<sup>37</sup>

#### *New treatments*

One strategy for counteracting the effects of hypercortisolaemia, used with some success makes use of the adrenal steroid dehydroepiandrosterone (DHEA).<sup>6</sup> According to Wolkowitz et al.,<sup>51</sup> DHEA is the most abundant corticosteroid in humans. Its physiologic role, however, as well as of its major metabolite, DHEA-S, remains unknown. Besides being a testosterone and estrogen precursor (both mood-affecting), DHEA seems to be involved in mood regulation and well-being improvement. It has also antiglucocorticoid properties that counteract the cortisol-induced effects and increase the levels of serotonin in some brain regions. Side-effects reported are: oily skin, acne and less frequently, hirsutism and deepening of the voice.<sup>50</sup>

The high levels of cortisol concentration can be lowered pharmacologically, with medication that inhibit the synthesis of steroids, such as ketoconazole, aminoglutethimide and metyrapone.<sup>6</sup>

Wolkowitz et al.<sup>52</sup> have reported that the use of ketoconazole is associated to the enhancement of depressant symptoms only in hypercortisolemic (n = 8) not in eucortisolemic patients (n = 12). Those data suggest that patients with elevated levels of cortisol have a better response to treatment with ketoconazole than those with normal levels.<sup>52</sup> Even though the author has

found an improved therapeutic result in hypercortisolemic patients in the same study, there was no significant reduction of cortisol levels during treatment with ketoconazole. This finding would give room for questioning if the antidepressant effects are not associated with other adrenal steroids.<sup>53</sup>

In a 4-week study<sup>53</sup> with bipolar disorder patients, type I or type II (n = 6), aged between 18 and 65, treated with ketoconazole, no plasma cortisol reduction was found, the same was found in a study by Wolkowitz et al.<sup>52</sup> However, none of the patients had elevated levels of cortisol in the beginning of the study and presented clinical improvement with ketoconazole, which differs from the study by Wolkowitz et al.<sup>52</sup>

Unfortunately, a limiting factor of the therapeutic use of the cortisol synthesis inhibitors is the high occurrence of side effects, which include, according to Wolkowitz & Reus:<sup>9</sup>

- **ketoconazole:** nausea, diarrhea, menstrual irregularities, abdominal discomfort, headache, reversible increases in serum transaminase levels, and, less commonly, vomiting, decreased libido, gynecomastia and impotence (both reversible);

- **metyrapone:** nausea, headache, sedation and rash;

- **aminoglutethimide:** somnolence, dizziness, fever, headache, and more rarely, goiter, hyperthyroidism, cholestasis, bone marrow suppression, and aldosterone deficiency.

Significant side effects are seen in two-thirds of patients treated with aminoglutethimide.

Preclinical studies indicate that CRH antagonists will be of use in clinical conditions related to HPA hyperactivity, particularly anxiety disorders.<sup>6</sup> Significant reductions in depression and anxiety scores was observed with CRH(1) receptor antagonist R121919 (doses between 5mg and 80mg/day), in an open study with 24 patients during 30 days, with a major depressive diagnosis as defined in the DSM-IV.<sup>54</sup>

Another strategy used to decrease cortisol is the activation of the negative feedback mechanism mediated by GRs, because they regulate the levels of cortisol: low doses of dexamethasone (3 – 4mg daily for 4 days).<sup>55</sup> Within these doses, dexamethasone does not break the blood-brain barrier and, consequently, the central GRs are saved from its glucocorticoid effect.

Only the GRs at the hypophysis level are activated, which decreases the levels of cortisol.<sup>55</sup> If the treatment with dexamethasone really decreases the endogenous cortisol, its efficacy can be associated with the patient's response to the suppression test with dexamethasone.<sup>6</sup> Some advantages with the use of this antagonist of GRs are: quick response, which reduces morbidity; low risk of suicide with dexamethasone overdose; no toxicity or side-effects with low doses and short-term treatment.<sup>55</sup>

On the other hand, the use of GR antagonists has also been studied and they have shown antidepressant effects, because it blocks the deleterious effects of the increased levels of cortisol and because it would produce an upregulation of these receptors.<sup>6,53,56</sup> A small double-blind controlled study<sup>56</sup> carried out with patients with psychotic depression using mifepristone (RU 486 – an antagonist of progesterone receptors that in high doses blocks GRs, showed that effects on psychotic symptoms were clinically more significant than the reduction of depressant symptoms. After RU 486 administration, the cortisol levels increased due to the reduction of the negative feedback mechanism and later normalized. The normalization of the HPA-axis functions can be associated to clinical improvement.<sup>56</sup>

Some new selective GR antagonists (ORG 34850, ORG 34116 and ORG 34517) have been developed, but some of them are not effective in the upregulation of these receptors.<sup>57</sup>

## CONCLUSION

The association between the use of glucocorticoid drugs and the onset of psychiatric symptoms is well documented, even though further studies are required to provide a clear relation between HPA-axis alterations and psychiatric disorders.

HPA-axis alterations are reported to be associated with mood swings, cognitive deficits and psychotic symptoms. As a consequence, a number of studies has been accomplished with the objective of studying possible therapeutic strategies that are able to act on hormonal dysfunctions produced by those swings, the effects of hypercortisolemia being the main focus of those studies.

The corticoid dose reduction is the first-choice treatment for psychiatric disorders secondary to those drugs. However, patients who can not discontinue the intake of corticoids require psychiatric medications: antipsychotic, antidepressants and mood stabilizers, depending on symptoms. The Tricyclic antidepressants are indicated for the treatment of glucocorticoids withdrawal depression, as they can cause agitation and psychosis, besides having a low response in patients with depression using corticoids.

Some studies have been using glucocorticoids antagonist synthesis drugs: ketoconazole, metyrapone and aminoglutethimide; CRH antagonists: R121919; glucocorticoids: low-dose dexamethasone and GR antagonists: RU 486, ORG 34850, ORG 34116 and ORG 34517. Further studies are still required for the determination of efficacy and safety of those treatments.

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## ABSTRACT

*The objective of this study was to make a literature review on associations between high plasma levels of corticosteroids and psychiatry symptoms, as well as to identify the most common clinical manifestations and treatments suggested. Hipercortisolemia resulting from alterations in the HPA axis would be associated with mood disorders, especially depression, whereas the use of glucocorticoid drugs would be related to the occurrence of psychiatric symptoms such as mania, depression, affective lability and psychosis. The review was performed via Medline and Bireme indexes, and articles published in English, French and Spanish between 1993 and 2003 were included. The following keywords were used: cortisol, corticosteroids, depression, bipolar disorder and psychosis. Original (33) and review (22) articles were included in the review; case reports were excluded.*

*Some studies suggest that long-term high plasma cortisol concentrations may cause depression, and that the use of antiglucocorticoid drugs would have an antidepressant effect. On the other hand, other studies do not show association between hypercortisolemia and depressive episodes.*

**Keywords:** *Cortisol, corticosteroids, depression, bipolar disorder and psychosis.*

**Title:** *The role of glucocorticoids in the modulation of mood symptoms – a review*

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