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Mood Disorders Associated with Glucocorticoid Therapy: Causes, Mechanisms, and Remediation

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ABSTRACT:Glucocorticoids are widely used in modern medicine for the treatment of a variety of inflammatory diseases. However, the side effects of glucocorticoid treatment often include neuropsychiatric illnesses. This systematic literature review gives a brief introduction to glucocorticoids, their functions, and possible mechanisms of how they lead to psychiatric side effects. After a review of the literature, it can be concluded that patients, as well as physicians prescribing glucocorticoids, should be aware of the potential side effects of glucocorticoid therapy, the means of adverse effect prevention, and efficacious treatments of psychiatric adverse effects. The first line of treatment is dose reduction or stopping the drug. The corticosteroid-induced mania can typically be treated with antipsychotics or mood stabilizers like haloperidol, olanzapine, valproate, lamotrigine plus clonazepam. Corticosteroid-induced depression can be treated with lithium alone or lithium added to fluoxetine, venlafaxine, and low-dose fluvoxamine. Due to the lack of psychiatric assessment in large studies, generalization of data is difficult, and the risk factors and exact mechanisms behind these side effects remain unknown. Future studies should be directed towards gene mapping to help identify risk-promoting roles for certain genes, as well as genes involved in the possible signal transduction pathways to induce these neuropsychiatric side effects.

KEYWORDS: Behavioral and social sciences; Neuroscience; corticosteroid; psychosis; BDNF.

Introduction

Glucocorticoids (GCs) are immunosuppressive and anti-inflammatory steroid hormones secreted by the cortex of the adrenal glands and regulated through the hypothalamic-pituitary-adrenal axis (HPA Axis). The HPA Axis activity is increased upon physiological and emotional stress due to an increase in endogenous GCs.[1] When the HPA Axis is stimulated, corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are released from the hypothalamic paraventricular nucleus (PVN).[1]CRH and AVP then binds their receptor CRH-R1 and V1B in the anterior pituitary, inducing the release of adrenocorticotropic hormone (ACTH) into the blood circulation. Subsequently, ACTH stimulates the adrenal gland via MC2-R (type 2 melanocortin receptor), to synthesize and secrete GC hormones into the bloodstream.[1] Figure 1 shows the workings of the HPA Axis. The HPA axis is subject to negative feedback inhibition by GCs. The genomic feedback regulation is mediated through the binding of the GCs to the glucocorticoid receptors (GRs) at the level of the PVN and the pituitary gland.[1] This represses the CR, CRH-R1, and the proopiomelanocortin (POMC) gene, which is the precursor of ACTH. The POMC gene expression is repressed by the binding of the GR to negative glucocorticoid responsive elements (nGREs)[2] and prevents it from performing its transcription functions, thus preventing more GC production. Non-genomically, GCs regulate the HPA axis via the release of endocannabinoids from CRH neurons, suppressing the subsequent release of glutamate from presynaptic excitatory synapses[3] or via GABA release at the inhibitory synapses of CRH neurons.[4] Once secreted, GCs are bound to and transported by plasma proteins.[1] Due to their lipophilic nature, GCs diffuse through the cell membrane and exert their effects.[1] Their non-polar covalent structure enables them to cross the blood-brain barrier and carry out their functions. GCs have a high affinity for brain mineralocorticoid receptors (MRs) and a low affinity for GRs.[5] GRs are expressed in virtually all organs and tissues, while MRs are located in both epithelial and nonepithelial tissues. GR functions by regulating the expression of GC-responsive genes in a positive or negative manner.[1] GCs are instrumental in the normal functioning and homeostasis of the Central Nervous System (CNS). GCs are used in the treatment of a wide variety of inflammatory conditions like allergies, back pain, dermatological, and ophthalmic conditions, gastrointestinal disorders, cancer, and lupus amongst others.[6] They influence both pro-inflammatory and anti-inflammatory cytokine secretion, thus exerting an important modulatory role on the immune system.[7] The degree of cortisol responsiveness has an important effect on susceptibility and resistance to inflammatory, autoimmune and infectious diseases.[7]

Discussion

Side effects of glucocorticoids:

Glucocorticoids, though used to suppress inflammation, are associated with numerous supraphysiological side effects including mood disorders, cognitive impairment, suicidal ideation, and anxiety.[8] GCs are secreted by the adrenal cortex. Excess endogenous glucocorticoid secretion or administration is known to cause Cushing's syndrome, with symptoms of obesity, weakness, osteoporosis, salt and water retention, and hyperglycemia.

Corticosteroid-induced reversible, anti-psychotic, cognitive deficits usually involve declarative and verbal memory, attention, and concentration.[9] These mild cognitive symptoms are

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experienced during short-term exposure to corticosteroids like dexamethasone and prednisone.[8] However, in severe cases, formal IQ may be substantially reduced and occupational performance and the ability to perform various tasks, skills, and activities may be diminished.[9] Although disturbances of mood, cognition, sleep, and behavior as well as frank delirium or even steroid-induced psychosis are possible, the most common adverse psychiatric effects of short-term corticosteroid therapy are euphoria and hypomania, occurring in temporary spells. Conversely, long-term therapy tends to induce depressive symptoms like manic behavior and psychosis. Some patients experience subtle mood disturbances, especially lability and irritability.[10] In addition to these effects, a decrease in the duration of REM sleep, and loss of brain hippocampal volume are also observed.[6] Treatment of these side effects includes adjusting the dosage or discontinuation of the corticosteroid treatment, prescribing antipsychotics, mood stabilizers such as lithium, and antidepressants.[8] Educating the patients and their families on possible side effects helps in the management of these disorders.[8]

Impact on memory, cognition, and behavior:

Corticosteroid-induced cognitive deficits without psychotic symptoms include declarative or verbal memory, and effects on concentration, recall, and analysis (steroid dementia). This is due to dysfunction in neural circuits in the hippocampus and prefrontal cortex.[11,12] Working memory is dependent on the prefrontal cortex and is involved in the tempo storage of information. This is necessary to carry out cognitive tasks like learning and reasoning.[13,14] Declarative memory, involved in the recall of verbal information, is dependent on the hippocampus.[15,16] Deficits in these functions could be the effect of prolonged GC exposure on GRs and MRs on the hippocampus due to the reduction of hippocampal volume[16] or excess glutamate accumulation in that area.[17] Declarative memory is also affected due to increased blood flow in the medial temporal lobe during GC therapy.[18] Reversible deficits in declarative memory have been reported in Cushing's disease and are greater in more severe cases.[19,20] This suggests that excess endogenous and exogenous corticosteroids produce similar cognitive impairment. Reversible cognitive deficits and mood symptoms have been observed in healthy control subjects after administration of prednisone, dexamethasone, and cortisol.[21-24] In healthy subjects, acute GC administration is associated with changes in several brain areas, decreased activity in the left hippocampus, reduced hippocampal glucose metabolism, and reduced cerebral blood flow to the posterior medial temporal lobe.[25-27] Also noted was atrophy of the right amygdala, which is an important regulator of mood and anxiety. This was correlated with the duration of prednisone treatment in a sample study.[28] Thus, excess GCs, endogenous or exogenous, have extreme ramifications on memory, cognition, and behavior.

The following excerpts from case studies have been adapted from Kenna *et.al* [8] and Judd *et.al* [6] to illustrate some of the neuropsychiatric side-effects of GC treatment and the difficulties that may be encountered in treating these.

1. Mrs. S, an 85-year-old widow, socially active woman with no prior psychiatric history, developed temporal arthritis with abrupt and permanent loss of vision in her right eye and blurred vision in her left. She developed significant depressive and psychotic symptoms that resulted in her hospitalization for apparent steroid-induced psychosis. The psychosis resolved several weeks later, and the patient was discharged but continued to become increasingly depressed. Her depressive symptoms were marked as anhedonia, apathy, and poor concentration, and she was disheveled in appearance with poor grooming and loss of function. Although her prednisone dose was lowered to 10 mg/day, she continued to decline. Four months later, after making suicidal statements and becoming assaultive toward her 24-hr caregiver, she was hospitalized again, this time for almost 2 months. She was severely depressed, hopeless, and nihilistic, with delusional guilt, visual hallucinations, poor insight, and self-neglect.

2. A married 50-year-old Caucasian woman began experiencing depression, intense fatigue, malaise, weight gain, and swelling of her lower extremities. She sought medical treatment and was found to have a pedal enema, azotaemia, and proteinuria. A renal biopsy showed acute focal and segmental glomerulosclerosis that was typical in its presentation. During the first prednisone cycle, the patient became, as she described it, "higher than a kite." She recalls being unable to sleep, lacking impulse control, and being inappropriately humorous. Her mind was flooded with unrelated thoughts, and her thinking became so disorganized that she was unable to drive. She had marked memory problems and required multiple reminders, including some pinned to her clothes, for various responsibilities and appointments. Her physician had explained that she might become "hyperactive" during prednisone treatment, but she was neither prepared for the magnitude and extent of the changes she experienced during the first cycle, nor for the depression that occurred during the first taper period and those in the other two treatment cycles.

The onset of psychiatric symptoms and their correlation with dosage:

Psychiatric side effects of corticosteroid treatment are known to have a rapid onset. A study reported a median time to onset of symptoms as early as 11.5 days.[29] Another study noted that 86% of patients developed psychiatric symptoms within a week of starting treatment.[30] Yet another study showed symptoms of corticosteroid treatment generally occurred within 2 weeks.[31] The corticosteroids dexamethasone and beta-methasone have half-lives of 36-54 hours[32] and can thus accumulate and induce psychiatric symptoms that begin after the last dose has been given.[33,34] These studies show that the psychiatric effects of GCs are immediate.

A study by the Boston Collaborative Drug Surveillance Program showed a dose-response correlation between corticosteroids. Chan *et.al* [35] showed a similar correlation in which they observed psychosis in 8% of patients receiving prednisone 90mg per day compared to 35 of patients receiving 30mg per day. Recent literature confirms the dose-response correlation of psychiatric symptoms. Olsen *et.al*[36] found a significant correlation between mood lability and prednisone

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dose in mg/kg six-week week taper from 40mg/d to zero in 32 patients with alopecia areata. In almost all of the literature on corticosteroid-induced dementia, the corticosteroid dose has been at least 60mg/d of prednisone equivalent, suggesting 60mg/d as a dose threshold in the induction of psychiatric symptoms.

Risk factors:

Researchers have found that women are more susceptible to developing depressive symptoms during initiation of oral glucocorticoid treatment, while men are more prone to developing delirium, mania, confusion, and disorientation.[6] This could be due to the sex hormone status and the influence of estrogenic and progesterone on the hypothalamic-pituitary-adrenal axis (HPA Axis).[7] The risk of delirium, depression, mania, confusion, and disorientation also increases with age.[6] Risk of suicide attempts, panic disorder, and depression increase with people with past histories of mental illness.[6] The risk of recurrence of the disorder during glucocorticoid exposure increases with the experience of a psychiatric disorder during glucocorticoid therapy.[6] Risk of psychiatric disorders in response to GC use is also dose-dependent. The presence or absence of previous psychiatric side effects does not predict responses to subsequent courses of corticosteroids i.e. a patient who has not shown any psychiatric side effects previously may still show side effects to a subsequent course of GCs. Corticosteroid-induced symptoms typically resolve with dosage reduction or discontinuation of corticosteroids.

Glucocorticoid availability at the molecular level:

Once GCs are released, there are factors responsible for the regulation of their availability to produce the required GC response. Some factors may modulate how GCs impact these adverse effects. These include corticosteroid-binding globulin (CBG), the multidrug resistance transporter (MDR), and 11β-hydroxysteroid dehydrogenase (11β -HSD), all regulated at the tissue and cell-specific level.[7] The relative concentration of these factors can dictate the availability of active GCs carry out their functions. These factors are altered under conditions of immune activation, as well as stress and antidepressant treatment.[7] 90% of circulating GCs are bound to CBG,[37] and thus the relative concentration of CBG is an important determinant of free GC. GCs exert their effects by diffusing across the cell membrane and binding to cytosolic receptors, however only unbound GCs are capable of diffusing across the membrane.[7] Previous studies have shown that stress and hypercortisolemia are associated with lower CBG concentrations,[38] while patients who responded to antidepressant amitriptyline were reported to have increased CBG levels.[39]

Modulation of MDR expression or function is also responsible for GC activity. The MDR, P-glycoprotein (Pgp), is an ATP-dependent multidrug efflux pump expressed in several tissues like the brain, liver, kidney, intestines, and adrenal glands.[7] At the blood-brain barrier, the MDR transports cortisol and the synthetic GC, dexamethasone, but not corticosterone out of the endothelial cells lining the brain.[40,41] Patients with various autoimmune diseases such as rheumatoid arthritis (RA), Crohn's disease, and lupus, exhibit high lymphocytic MDR expression and/or activity, which positively correlates with disease activity. Greater MDR expression in immune cells reduces GC availability, enhancing the synthesis and release of pro-inflammatory cytokines and increasing the inflammatory response.[7] This increased MDR expression may be secondary to treatment with high-dose GCs.[7] Altered MDR expression or function has been shown to contribute to depression.[7] Studies have demonstrated different types of antidepressants, increase GC availability in cells by inhibiting MDR function, thereby possibly reducing GC resistance.[42,43]

11β -HSD regulates GC availability by acting as a shuttle in converting GCs between their active and inactive forms. GC metabolism is mediated by 11β -HSDs. The 11β -HSDs type1 isoform acts as a reductase, converting inactive GC (cortisone) to active GC (cortisol), thus elevating cortisol levels. The type 2 isoform acts as an oxidase/dehydrogenase and inactivates GCs by converting cortisol into the inactive cortisone molecule.[44] Pro-inflammatory cytokines such as TNF- α and IL-1β have been shown to upregulate 11β -HSD 1 and downregulate 11β-HSD 2, thus favoring the formation of active GCs and controlling inflammation.[45] Enhanced expression of 11β-HSD2 or reduced expression of 11β-HSD1 has been demonstrated in autoimmune patients and could be another possible mechanism underlying GC resistance in such diseases.[7]

Too much or too little influence of GCs on mood, memory, and neuronal integrity can exert negative effects. Central 11β-HSD1 expression is high in areas that influence cognition and GC negative feedback on the HPA axis, such as the cerebellum, hippocampus, prefrontal cortex, PVN of the hypothalamus, and pituitary gland.[7]

Glucocorticoid receptor action in modulating glucocorticoid effects:

The GR belongs to the nuclear receptor superfamily of transcription factors (TFs) and is a 97 kDa protein that is expressed throughout the body.[1] They regulate gene expression by either direct interaction with specific promoter sequences called glucocorticoid response elements, or through protein-protein interactions with other transcription factors, such as NF-kB, AP-1, STAT, and NFAT.[46] There have been several polymorphisms identified in the human GR gene which may be associated with hypo or hyper function of the receptor, contributing to differential individual sensitivity to the effects of GC treatment.[7] Some polymorphisms are related to an increase or decrease in GC sensitivity and have been associated with altered susceptibility, to metabolic disorders, cardiovascular disease, autoimmune and infectious disease, neuroendocrine responses to stress, as well as altered cognition and effect.[7] Recent genetic studies have shown certain polymorphisms like Bc/1 and ER22/23EK, are associated with increased susceptibility to developing major depression, and the ER22/23EK polymorphism is associated with a faster response to antidepressants.[47,48] The polymorphism of the GR gene NR3C-1, in the promoter region, has been associated with increased susceptibility to depression.[49]

In the absence of intracellular bioactive GCs, the GR is a monomer in the cytoplasm where it resides in a multiprotein complex.[1] This chaperone complex is important for GR maturation, ligand binding, nuclear transport, and activation.[1] The composition of the chaperone complex changes during the different GR maturation/activation states.[50] Once inside the nucleus, the activated GR can go on to exert its function or it can be transported back to the cytoplasm, inhibiting the GR's transcriptional activity.[1] Nuclear export of GR is regulated by exportins and calreticulin (CRT) which bind to the GR NES, thereby disrupting the GR-DNA binding.[51,52] The balance between nuclear import and export determines the proportion of GR protein in the nucleus and has a direct influence on the strength of GR's transcriptional activities.[1] In the nucleus, the GR acts as a TF that can activate (transactivation) or inhibit (trans-repression) genes as well as modulate the function of other TFs (tethering).[1]

Sensitivity to GC action at the level of the GR can be determined by factors such as GR number, affinity, and function, including its ability to translocate to the nucleus and its interaction with other signal transduction pathways.[53,54] In addition, sensitivity to GCs depends on the expression of particular GR isoforms.[7] GRα mediates GC action, while GRβ and GR-P have been shown to mediate GRα activity and are unable to bind ligands.[7]Generally, GRβ is expressed at very low levels compared to GRα; however, its expression is increased in tissues in inflammatory diseases, and it seems to be associated with decreased sensitivity to GCs.[55] Increased GRβ expression may be related to impaired negative feedback mechanisms mediated by GRα activity and has been associated with the development and/or aggravation of symptoms in various glucocorticoid-resistant diseases, such as asthma, colitis/Crohn's, and RA.[53] Moreover, changes in expression and stability of different GR isoforms can be triggered by inflammation[56] and have also been associated with mutations or polymorphisms in the receptor.[54,57,58]

Possible mechanisms

Role of MRs and GRs in the brain-structure function analysis:

GCs penetrate the brain and bind to 2 types of receptors: GRs, expressed in cerebral neurons and glial cells, and MRs, which GCs have a higher affinity for, and are expressed in limbic brain areas like the hippocampus, which control the temperature of the body and the pituitary gland.[44] MRs have a higher affinity for endogenous corticosteroids and have been associated with cortisol-related circadian variations, while GRs have a higher affinity for dexamethasone.[7]

GRs have a lower affinity for endogenous corticosteroids, but they are activated when endogenous GC levels are high. Low cortisol levels occupy MRsd, but when GC concentrations are high, GRs are also activated since there are enough GCs to activate MRs and GRs.[44] GCs exert their effects by binding to cytosolic MRs and GRs and then translocate to the nucleus upon binding to their ligand.[59,60] The circadian cycle is a natural internal process that regulates an individual's sleep-wake cycle. The activation of both GRs and MRs occurs during the active period of the circadian cycle and in Cushing's syndrome.[7] In hippocampal cells, only 11β-HSD type 1 is expressed, which converts inactive cortisone to active cortisol.[7] Thus there is conversion to active cortisol in these areas and since the type 2 isoform is not expressed in the hippocampus and other limbic areas, there is only active cortisol circulating, leading to MR activation by GCs in these areas, and possibly explaining the changes seen in these areas during chronic exposure to GCs.[7]

GCs and neurons:

Chronic exposure to GCs inhibits regenerative sprouting of axons that follows differentiation of hippocampal neurons and reduction in the number of these neurons.[44] Brain-derived neurotrophic factor (BDNF) is involved in many functions such as neuronal growth, survival, synaptic plasticity, and memory formation and protects against stress-dependent impairment of spatial memory. Figure 2 (shown below) illustrates the cytokine-mediated repression of BDNF, and the subsequent repression of the genes involved in neuronal architecture.

It is thus important for maintaining neural architecture in brain regions such as the hippocampus and prefrontal cortex.[44] Pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α play a functional role in the CNS by increasing glutamate release and decreasing the expression of glutamate transporters on relevant glial elements, releasing in decreased glutamate uptake.[61] Glutamate downregulates the expression of BDNF.[61] The cytokine mechanism provides a possible explanation for stress-related changes. Under normal physiological conditions, these cytokines give support to neurons, helping in neurogenesis and contributing to normal cognitive function.[61] However, stress-induced prolonged activation of these cytokine networks can also lead to abnormalities consistent with neuropsychiatric disorders. These include decreased neurogenesis, increased glutamatergic activation, oxidative stress, induction of apoptosis in astrocytes and oligodendrocytes, and cognitive function.[62] The pathway to these effects, especially concerning behavior, requires cytokines and inflammatory mediators to increase glutamate release and to decrease the expression of glutamate transporters on relevant glial elements, resulting in decreasing glutamate reuptake.[61] Neuroimaging techniques have provided insight into the correlation between neuroinflammation, glial dysfunction and glutamate synaptic dysfunction in depressed patients.[62] Glutamate regulates synaptic transition and plasticity by activating glutamate receptors (AMPA, NMDA, mGluR1 to mGluR8).[63] Glutamate is cleared from the extracellular space by high-affinity excitatory amino acid transporters (EAATs) which are located on neighboring glial cells.[63] Glutamate is converted to glutamine by glutamine synthetase. Glutamine is then transported back into the glutamatergic neuron, where it is hydrolyzed into glutamate by glutaminase.[63] There are no degradative enzymes in the synapse and therefore uptake by EAATs is the primary mechanism through which the action of extracellular glutamate is terminated.[63] Acute stress and GCs induce extracellular glutamate levels, possibly due to decreased ability to clear extracellular glutamate as a result of impaired glial cell uptake and metabolism, combined with

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stress-related changes in glutamate release,[63] thus raising extra-synaptic glutamate levels. Pre-synoptically, this suppresses glutamate release and post-synaptically reduces synaptic connectivity by overstimulating the NMDA receptors.[64]

Thus, GRs target glial cells by inducing glutamine synthetase activity, which converts active glutamate to inactive glutamine. This allows glutamate synthesis to reoccur in cultured astrocytes, inducing an increased release of glutamate[65-67] that induces neuronal toxicity due to the accumulation effect.[68] Abnormally high concentrations of glutamine of the receiving nerve cell can lead to effects that can cause cell damage and/or death. Animal model data suggests that N-methyl-D-aspartate (NMDA) receptor antagonists or glutamate release inhibitors (phenytoin) may block the corticosteroid effect on the hippocampus.[69] Decreased neurogenesis in the hippocampus of rats was also observed due to increased corticosterone levels induced by sleep deprivation.[70] MRS spectroscopy studies have shown characteristic reductions in glutamatergic and GABAergic neurotransmission in depressed patients.[71] The astrocyte-released glutamate acts on the extra synaptic NMDA receptors to mediate excitotoxicity, and to decrease the production of trophic factors including BDNF,[61] explaining why GRs downregulate BDNF expression, resulting in a consequent loss of spatial, verbal, and declarative memory in patients treated with exogenous GCs, and also contributing to the development of depression and anxiety.[72] Since GCs stimulate apoptosis of hippocampal neurons, chronic hypercortisolemia also leads to atrophy and cell death.[73] Cytokines, TNF-α, and IL-1 also cause astrocytes and microglia to release reactive oxygen and nitrogen species, causing an amplification of oxidative stress.[61] Thus astrocyte and microglial release of cytokines contribute to the amplification of inflammatory pathways within the brain. This leads the to loss of glial elements, oligodendrocytes, and astrocytes involved in multiple mood-relevant brain regions, including the prefrontal cortex, which is associated with the control of working memory, and the amygdala, which is associated with the body's response to stress and fear and plays a pivotal role in memory. These have emerged as fundamental morphologic abnormalities in patients with depression.[61]

In patients with Cushing's syndrome, lower brain weight, loss of brain volume, and ventricular enlargement were observed.[74-78] Hippocampal volume was also reduced in a large proportion of patients.[79-81]

HPA Axis dysfunction:

GC's are involved in glucose metabolism, inflammation, and immunity.[5] GCs have important effects on arousal, memory, and cognition as well as fetal development and aging[6] The stress-responsive PA Axis regulates GC production, and its dysfunction is implicated in the pathophysiology of anxiety, depression, and psychotic disorders related to chronic exposure to GCs.[7] Hypothalamic secretion of the corticotropin-releasing factor (CRF) stimulates the release of corticotropin (ACTH) from the anterior pituitary and the subsequent release of cortisol from the adrenal glands. The rapid effects and feedback to the hypothalamus which follow are mediated by the MRs and GRs.[6] Synthetic GCs used in treatment preferentially activate pituitary GRS, causing suppression of ACTH and preventing endogenous cortisol release.[6] Hence synthetic GCs activate GRs in the brain while depleting cortisol from MRs.[82] Prolonged application of high doses of corticosteroids can thus lead to HPA axis dysregulation. Major depressive disorder is associated with dysregulation of the HPA axis. HPA axis dysfunction, reported in patients with depression, is believed to be partly related to impaired feedback inhibition by endogenous GCs due to GC resistance[83] or due to hypersecretion of CRH.[84,85] This is due to a lack of inhibition of ACTH responses to CRH following dexamethasone pre-treatment, which points to an impaired feedback inhibition at the level of the pituitary.[7] Central 11-beta-HSD-1 expression is high in areas that influence cognition, thus possibly affecting the GC induced negative feedback mechanism of the HPA axis in areas such as the prefrontal cortex, cerebellum, hippocampus, PVN of the hypothalamus, and pituitary gland.[7] 11-beta-HSD levels have been shown to be associated with depression in certain studies, but the results are inconclusive.[86] Thus both exogenous use of high dose steroids and endogenous excess of these hormones are associated with mood disorders and depressive symptomatology, the mechanisms of which are unknown. Resolution of impaired HPA Axis function, due to administration of exogenous GCs, could cause a reduction of these disorders.

The information about infection or injury is conveyed to the brain, which sets off various mechanisms directed toward the restoration of health and homeostasis. Cytokines are chemical messengers derived from immune cells, which act as immunomodulators and neuromodulators, and mediate many of these functions. They can be classified into pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor (TNF), augment the immune response to help remove pathogens and dispel the inflammatory challenge. Anti-inflammatory cytokines like interlukin-4-10 (IL4-10) and interleukin-13 (IL-13), dampen the immune response. The physiological and psychological effects of immune activation during infection, which are primarily mediated by the central effects of peripherally released pro-inflammatory cytokines, are collectively referred to as sickness behavior. The behavioral responses observed during infection are observed in patients after receiving their systematic administration of cytokines. Immunotherapy with IFN-α, a pro-inflammatory cytokine, has been associated with symptoms of cognitive impairment, fatigue, behavioral despair, and depression. The symptoms of sickness behaviour almost immediately disappear after terminating cytokine administration, suggesting a causal role for cytokines in mediating this condition. Alteration in the pro-inflammatory cytokine milieu can lead to behavioral changes, which are similar to those found in patients with depressive symptoms including altered sleep patterns, anhedonia, decreased activity, and cognitive dysfunction. The change of pro-inflammatory mediators is seen as a trigger of depression. There is a bidirectional relationship between the immune system and

the HPA axis in which cytokines stimulate the HPA axis, releasing

GCs which provide negative feedback control of the immune system, thus keeping a check on the inflammation.[87-89] GCs prevent the production of pro-inflammatory TH1 cytokines and increase the production of anti-inflammatory TH2 cytokines.[90] IL-6 is the primary relevant pro-inflammatory cytokine. Cytokines can stimulate the HPA Axis by acting on the brain, the pituitary, or the adrenal gland.[7] Studies have shown that pro-inflammatory cytokines can induce GC resistance by reducing GC function.[91] Reduction of GR function and affinity induced by cytokines has been found in patients with inflammatory diseases, especially those exhibiting resistance to GC treatment.[91] Reduced GR function contributes to enhanced pro-inflammatory cytokine production, associated with the development of depression.[7] There is an inverse correlation between the serum level of IL-6 and the precursor of serotonin, which is the key hormone that stabilizes our mood, feelings of happiness, and well-being.[92] Serotonin enables brain cells and other cells in the nervous system to communicate with each other and it helps with sleeping, eating, and digestion. IL-6 in depressive patients is higher.[93] Most studies on 'the cytokine theory of depression' are focused on increased levels of pro-inflammatory cytokines. The role of anti-inflammatory cytokines has been recently analyzed and a decreased IL-10 level in depressive patients has been observed[94] while confounding factors for cytokine, including certain chronic physical illnesses and medication. Hence, the elevated ratio of IL-6/IL-10 may be a contributing factor to depression.[61, 95]

Four antidepressant drugs, imipramine, venlafaxine, 1-5 hydroxytryptophan, and fluoxetine, have been found to increase the production of IL-10 (anti-inflammatory mediator).[61] Fluoxetine has been observed to lower the serum level of IFN-y (pro-inflammatory), whereas all four anti-depressants decreased the IFN-y/IL-10 ratio significantly.[61] The tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as the immediate precursor of serotonin, have a common, negative, immunoregulatory effect by suppressing the IFN-y/IL-10 production ratio.96 Antidepressants promote the production of IL-10, which in turn reduces the ratio of pro and anti-inflammatory mediators.[97] IL-10 was observed to alter the balance of TH1/TH2.[98]

Current treatments:

Psychiatric disturbances resulting from corticosteroid therapy commonly resolve slowly after discontinuation of the drug or reduction of the dosage.[99] Initial treatment of corticosteroid-induced psychiatric disturbances should follow this protocol.[99] For patients receiving high-dose and long-term treatment, a taper is advised to prevent both physiologic and psychiatric corticosteroid withdrawal phenomena.[100] An inappropriate taper can result in 3 types of difficulties: (1) suppression of the hypothalamic-pituitary-adrenal axis (HPA) with the potential for secondary adrenal insufficiency, (2) recurrence of the disease for which the therapy was initiated, and (3) a corticosteroid withdrawal syndrome characterized by symptoms of adrenal insufficiency but with normal HPA function.[101] Appropriate tapering is critical and should be based on total dosage, therapy duration, and corticosteroid type. For patients who cannot tolerate corticosteroid cessation or dose reduction due to the severity of the disease, or who suddenly develop psychosis, severe agitation, aggressive behavior, or other intolerable symptom complexes, palliative pharmacotherapy is indicated, even though no definitive treatment has been identified.[99] In certain patients, pharmacotherapy may prevent corticosteroid-induced psychiatric disturbances.[69] For example, anecdotal evidence suggests that lithium may be effective for the acute treatment of corticosteroid-induced psychiatric symptoms, including mania and depression.[102,103] Lithium increases the amount of certain chemicals in the brain which stabilizes mood. Some other studies suggest that valproic acid, neuroleptics and atypical antipsychotics can be administered for treatment of these symptoms.[104-108] Valproic acid increases GABA production in the brain. GABA blocks transmission across nerves in the brain and also has an anti-anxiolytic effect.

Case studies of treatments:

The following excerpts from case studies have been adapted from Kenna *et.al*[9] and Judd *et.al*[6] in order to illustrate some of the neuropsychiatric side-effects of GC treatment and the difficulties that may be encountered in treating these.

1. Mrs. S began oral prednisone. 60 mg/day. While tapering down to 40 mg/day 1 month later, she developed significant depressive and psychotic symptoms that resulted in her hospitalization for apparent steroid-induced psychosis. The psychosis resolved several weeks later and the patient was discharged, but continued to become increasingly depressed. Although her prednisone dose was lowered to 10 mg/day, she continued to decline. Four months later, after making suicidal statements and becoming assaultive toward her 24-h caregiver, she was hospitalized again, this time for almost 2 months. In hopes of saving the remaining vision in her left eye, methotrexate was added to her prednisone 10 mg/day. She was stabilized and discharged on olanzapine 7.5 mg alternating with 10 mg q.h.s., bupropion XL 300 mg/ day, duloxetine 90 mg/day, benztropine 0.5 mg q.h.s., and, lorazepam 0.5 mg bid p.r.n. Two weeks later upon follow up, Mrs. S was neatly groomed and cheerful. She denied depressed mood, anhedonia, and suicidality. In the following months, her mood remained stable and she resumed social activities while continuing her hospital discharge medications. Olanzapine and duloxetine were gradually decreased, while bupropion, benztropine and lorazepam were discontinued after 4 months.

In the case of Mrs. S, the corticosteroids could not be discontinued and therefore the use of psychotropic treatment was required which ultimately resulted in a good prognosis.

2. The patient was started on a cycle of prednisone, beginning with 70 mg/day and tapering by 5 mg per week until the dosage was 10 mg/day because of the renal biopsy. At 10 mg/day, the proteinuria returned, and the nephrologist decided to initiate another cycle of prednisone, with the same starting dosage and tapering schedule. Once again the

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proteinuria returned when the dosage reached 10 mg/day, and the patient underwent a third cycle of prednisone, with the same result. During this time, the patient was intensely anxious, and her nephrologist prescribed alprazolam in escalating doses up to 4 mg per day, which suppressed her anxiety. After the third course of prednisone failed to ameliorate the glomerulosclerosis, the patient was started on 100 mg/day of cyclophosphamide, to continue until her urine was free of protein. She was treated with cyclophosphamide for approximately 4 months, at which time she was free of proteinuria and was asymptomatic. She was discharged from treatment and has remained asymptomatic, with continued monitoring every 3 to 6 months. Three days after starting the first prednisone cycle, the patient became, as she described it, "higher than a kite." When her depression became severe, she sought treatment on her own from a psychiatrist, who prescribed bupropion, which successfully treated the depression. Throughout the three treatment cycles, the patient's thinking remained disorganized, with memory difficulties and memory loss. These symptoms persisted for approximately 12 months, diminishing over time to the point that she was able to return to work and begin driving again. The patient continues to report experiencing memory problems, some loss of cognitive clarity, and a greater vulnerability to overreacting to stress.

This particular case study demonstrated, once again, the need for an antidepressant, in this case an SSRI, to treat the prednisone-induced depression. The patient showed deficits in cognition and memory after the first prednisone cycle itself. These symptoms however, diminished over time after discontinuation of the GCs, illustrating the possible reversibility of neuropsychiatric side-effects in some cases.

Future directions:

The literature on the treatment is limited to numerous case reports and a few small trials.[9] These provide clinical guidance, but require further studies.[9] The education of patients and their families about the risks of side-effects of GC therapy is imperative, especially since these adverse effects have a rapid onset.[9] The most common first-line treatment for GC induced neuropsychiatric symptoms is dosage reduction or discontinuation. Taper schedules, especially after long term GC treatment should be followed and patients need close monitoring for new or increased symptoms. When severe problems with mood, memory, cognition, or behaviour occur during GC treatment or withdrawal, a psychiatrist should be consulted. There are several recommendations for medication based on preliminary evidence from case studies and clinical trials. GC induced mania or mixed manic symptoms seem to respond to lithium carbonate,[9] olanzapine,[32] or phenytoin.[109] Sodium valproate appears to reverse manic-like symptoms rapidly while allowing GC treatment to continue.[110] Depressive symptoms improve with the use of selected SSRIs such as sertraline, fluoxetine, venlafaxine, and low-dosage fluvoxamine, as well as with lithium alone,[9] but not with tricyclic anti-depressants.

Speculation regarding mechanisms by which these drugs work include regulation of corticosteroid effects on dopaminergic and cholinergic systems[111,112] and modulating the decrease in serotonin release.[113] This is because corticosteroids, which regulate the activity of the raphe-hippocampal serotoninergic pathway, may affect the serotoninergic system and increase the risk for anxiety and depression.[5] A detailed, in-depth analysis of this particular pathway may prove beneficial in the future treatments of mental disorders. If the patient has underlined bipolarity, mood stimulators should be used instead of antidepressants to prevent switch into manic or mixed dysphoric states. GC induced psychosis can be prevented with atypical antipsychotics alone with lithium,[9] while GC induced delirium responds to haloperidol or atypical antipsychotics. Haloperidol can directly regulate the HPA axis and immune system through a pharmacological action via D2 receptor antagonism.[114] Memory problems induced by GCs in patients have been reduced by administration of lamotrigine[115,116] and by the NMDA receptor antagonist, memantine.[117] The beta-blocker propranolol has been found to block GC induced memory deficits in healthy subjects.[118]

Monitoring is an extremely high priority and prophylactic treatment should be considered for patients with recent history of mood or cognitive disorder. Prophylactic treatment should also be given to patients with autoimmune medical conditions like multiple sclerosis[119] and patients with other neurological disorders[120] that are characterized by mood or cognitive disturbances. These conditions may increases the risk of new onsets or exacerbations of such problems during GC withdrawal or treatment.

Since individual susceptibility to the serious mood and depressive effects of GC therapy could be due to individual variations at all levels of GC regulation, these avenues need to be further explored.[7] These include CRH signalling, GC hormone levels, factors regulating GC availability and the GR. GR polymorphisms conferring hypo or hyper sensitivity of the GR are equally important.[7] Moreover, the presence of immune activation, with excess TH1 cytokines could also contribute to HPA dysfunction and behavioural changes.[7] A closer look at these possible factors in patients requiring high dose GC administration, could reduce the risk of side-effects by effective management of these factors.

Conclusion

Corticosteroids are used in the treatment of many illnesses, but their psychiatric side-effects are of common concern to all physicians. Therefore, educating patients about these side-effects is essential. Each patient has a different level of susceptibility to neuropsychiatric effects of GC therapy, which can vary over time.[6] The risk factors include age, gender, genetic, and background factors at all levels of GC regulation, and the risk may be elevated based on an individual's past psychiatric history.[6] However, it is not possible to predict which patients will experience these adverse effects and therefore all patients should be considered at risk and monitored closely.[6] Very little data is available on the incidence and prevalence of these side-effects, and few studies have been performed.[6] The available data suggests that the psychiatric symptoms during GC therapy are dose-dependent with an early onset, and include mania, depression and psychosis.[6] Further studies on the mood and cognitive effects of GC therapy are needed.

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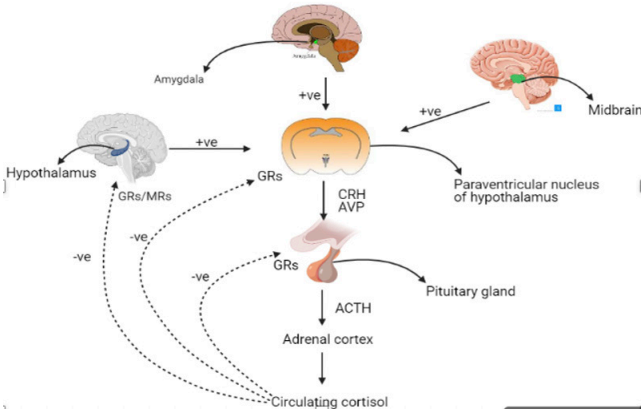

Figure 1: Shows the positive and negative interactions within the HPA Axis.

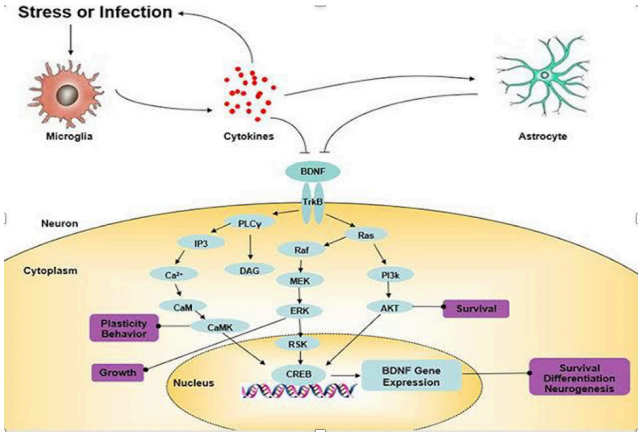

Figure 2: Shows the cytokine mediated repression of BDNF and the subsequent repression of the genes involved in neuronal architecture. The BDNF gene expression leads to survival differentiation neurogenesis. Akt, serine/threonine protein kinase; BDNF, brain-derived neurotrophic factor; CaM, calmodulin; CaMK, calcium-calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; IP3, inositol 1,4,5-trisphosphate; MEK, mitogen-activated extracellular signal-regulated kinase; PKC, protein kinase C; PI3K, PI-3 kinase; PLC-γ, phospholipase-Cγ; RSK, ribosomal S6 kinase; TrkB, tyrosine kinase B. (Yang *et.al*.121).

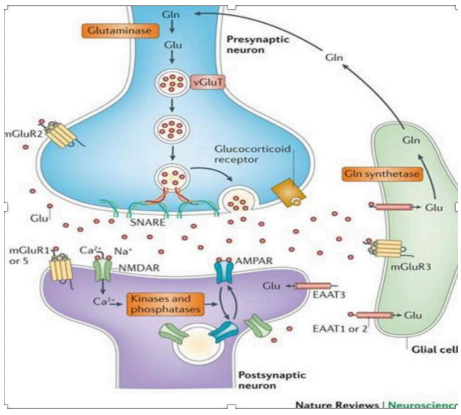

Figure 3: Neuronal glutamate (Glu) is synthesized de novo from glucose (not shown) and from glutamine (Gln) supplied by glial cells. Glutamate is then packaged into synaptic vesicles by vesicular glutamate transporters (vGluTs). SNARE complex proteins mediate the interaction and fusion of vesicles with the presynaptic membrane. After release into the extracellular space, glutamate binds to ionotropic glutamate receptors (NMDA receptors (NMDARs) and AMPA receptors (AMPARs)) and metabotropic glutamate receptors (mGluR1 to mGluR8) on the membranes of both postsynaptic and presynaptic neurons and glial cells. Upon binding, the receptors initiate various responses, including membrane depolarization, activation of intracellular messenger cascades, modulation of local protein synthesis and, eventually, gene expression (not shown). Surface expression and function of NMDARs and AMPARs is dynamically regulated by protein synthesis and degradation and receptor trafficking between the postsynaptic membrane and endosomes. The insertion and removal of postsynaptic receptors provide a mechanism for long-term modulation of synaptic strength. Glutamate is cleared from the synapse through excitatory amino acid transporters (EAATs) on neighbouring glial cells (EAAT1and EAAT2) and, to a lesser extent, on neurons (EAAT3 and EAAT4). Within the glial cell, glutamate is converted to glutamine by glutamine synthetase and the glutamine is subsequently released by System N transporters and taken up by neurons through System A sodium-coupled amino acid transporters to complete the glutamate–glutamine cycle. (Adapted from Popoli *et.al* (134)).

References

1. Timmermans S, Souffriau J, Libert C. A General Introduction to Glucocorticoid Biology. (July 2019) Vol.10 Article 1545
2. Malkoski SP, Dorin RI. Composite glucocorticoid regulation at a functionally defined negative glucocorticoid response element of the human corticotropin-releasing hormone gene. Mol Endocrinol. (1999) 13:1629–44. doi: 10.1210/mend.13.10.0351
3. Di S, Malcher-Lopes R, Halmos K, Tasker JG. Nongenomic glucocorticoid inhibition via endocannabinoid release in the hy pothalamus: a fast feedback mechanism. J Neurosci. (2003) 23:4850–7. doi: 10.1523/JNEUROSCI.23-12-04850.2003
4. Di S, Maxson MM, Franco A, Tasker JG. Glucocorticoids regulate glutamate and GABA synapse-specific retrograde transmission via divergent nongenomic signaling pathways. J Neurosci. (2009) 29:393–401. doi: 10.1523/JNEUROSCI.4546-08.2009
5. Thibaut F. Corticosteroid-induced psychiatric disorders: genetic studies are needed. European Archives of Psychiatry and Clinical Neuroscience 2019;269:623-625
6. Judd LL, Schettler PJ. Brown ES, Wolkowitz OM, Sternberg EM, Bender BG, Bulloch K, Cidlowski JA, Ronald de Kloet E, Fardet L, Joels M, Leung DYM, McEwen BS, Roozendaal B, Van Rossum EFC, Ahn J, brown DW, Plitt A, Singh G. Adverse Consequenc es of Glucocorticoid medication: psychological, Cognitive, and Behavioral Effects. Am J Psychiatry October 2014;171:10:1045-1051
7. Marques AH, Silverman MN, Sternberg EM. Glucocorticoid Dys regulations and Their Clinical Correlates: From Receptors to Ther apeutics. Ann N Y Acad Sci. 2009; 1179: 1-18.
8. Brown ES, Chandler PA. Mood and Cognitive Changes During Systemic Corticosteroid Therapy. Primary care Companion J Clin Psychiatry 3:1 February 2001; 17-21
9. Kenna HA, Poon AW, Paula de los Angeles C, Koran LM. Psy chiatric complications of treatment with corticosteroids: Review with case report. Psychiatry and Clinical Neurosciences 2011; 65: 549-560
10. Starkman MN, Schteingart DE, Schork MA. Correlation of bedside cognitive and neuropsychological tests in patients with Cushing's syndrome. Psychosomatics 1986; 27:508.
11. Wolkowitz OM, Burke H, Epel ES, Reus VI: Glucocorticoids: mood, memory, and mechanisms. Ann N Y Acad Sci 2009; 1179:19– 4
12. Weerda R, Muehlhan M, Wolf OT, Thiel CM: Effects of acute psychosocial stress on working memory related brain activity in

DOI: 10.36838/v4i5.4

men. Hum Brain Mapp 2010; 31:1418–1429
13.Oei NY, Everaerd WT, Elzinga BM, van Well S, Bermond B: Psychosocial stress impairs working memory at high loads: an as sociation with cortisol levels and memory retrieval. Stress 2006; 9:133–141
14.Zobel AW, Schulze-Rauschenbach S, von Widdern OC, Metten M, Freymann N, Grasmäder K, Pfeiffer U, Schnell S, Wagner M, Maier W: Improvement of working but not declarative memory is correlated with HPA normalization during antidepressant treat ment. J Psychiatr Res 2004; 38:377–383
15.Eichenbaum H, Otto T, Cohen NJ: The hippocampus: what does it do? Behav Neural Biol 1992; 57:2–36
16.Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ: Cortisol levels during human aging predict hippocampal atrophy and mem ory deficits. Nat Neurosci 1998; 1:69–73
17.Aulakh R, Singh S: Strategies for minimizing corticosteroid toxic ity: a review. Indian J Pediatr 2008; 75:1067–1073
18.de Quervain DJ, Henke K, Aerni A, Treyer V, McGaugh JL, Berthold T, Nitsch RM, Buck A, Roozendaal B, Hock C: Gluco corticoidinduced impairment of declarative memory retrieval is as sociated with reduced blood flow in the medial temporal lobe. Eur J Neurosci 2003; 17:1296–1302
19.Mauri M, Sinforiani E, Bono G et al. Memory impairment in Cushing's disease. Acta Neurol. Scand. 1993; 87: 52–55.
20.Starkman MN, Schteingart DE. Neuropsychiatric manifestations of patients with Cushing's syndrome. Relationship to cortisol and adrenocorticotropic hormone levels. Arch. Intern. Med. 1981; 141: 215–219.
21.Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. Glucocorticoid-induced impairment in declarative memory perfor mance in adult humans. J. Neurosci. 1994; 14: 2047–2053.
22.Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, Alderson AL. Decreased memory performance in healthy hu mans induced by stress-level cortisol treatment. Arch. Gen. Psychi atry 1999; 56: 527–533.
23.Wolkowitz OM, Reus VI, Weingartner H et al. Cognitive effects of corticosteroids. Am. J. Psychiatry 1990; 147: 1297–1303.
24.Wolkowitz OM, Rubinow D, Doran AR et al. Prednisone effects on neurochemistry and behavior. Preliminary findings. Arch. Gen. Psychiatry 1990; 47: 963–968.
25.Charbonneau Y, Ravindran AV. Successful treatment of steroid-in duced panic disorder with fluvoxamine. J. Psychiatry Neurosci. 1997; 22: 346–347.
26.Finkenbine RD, Frye MD. Case of psychosis due to predni sone-clarithromycin interaction. Gen. Hosp. Psychiatry 1998; 20: 325–326.
27.Sirois F. Steroid psychosis: a review. Gen. Hosp. Psychiatry 2003; 25: 27–33.
28.Brown ES, Chamberlain W, Dhanani N, Paranjpe P, Carmody TJ, Sargeant M. An open-label trial of olanzapine for cortico steroid-induced mood symptoms. J. Affect. Disord. 2004; 83: 277–281.
29.Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. J. Affect. Disord. 1983; 5: 319–332.
30.Hall RC, Popkin MK, Stickney SK, Gardner ER. Presentation of the steroid psychoses. J. Nerv. Ment. Dis. 1979; 167: 229–236.
31.Ling MH, Perry PJ, Tsuang MT. Side effects of corticosteroid therapy. Psychiatric aspects. Arch. Gen. Psychiatry 1981; 38: 471–477.
32.Clinician's Ultimate Reference. Available from URL: http://www.globalrph.com/corticocalc.htm (last accessed 19 August 2011).
33.Ferris RL, Eisele DW. Steroid psychosis after head and neck sur gery: case report and review of the literature. Otolaryngol. Head Neck Surg. 2003; 129: 591–592.
34.Galen DM, Beck M, Buchbinder D. Steroid psychosis after or thognathic surgery: a case report. J. Oral Maxillofac. Surg. 1997; 55: 294–297.
35.Chan L, French ME, Oliver DO, Morris PJ. High- and low-dose prednisolone. Transplant. Proc. 1981; 13: 336– 338.
36.Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. Arch. Dermatol. 1992; 128: 1467– 1473.
37.Rosner W. Plasma steroid-binding proteins. Endocrinol Metab Clin North Am 1991;20:697–720. [PubMed: 1778174]
38.Tinnikov AA, et al. Serum corticosteroid-binding globulin levels in children undergoing heart surgery. Steroids 1993;58:536–539. [PubMed: 8273117]
39.Deuschle M, *et al*. Increased concentration of corticosteroid-bind ing globulin due to antidepressant treatment with amitritpyline, but not paroxetine. J Psychiatr Res 2003;37:85–87. [PubMed: 12482473]
40.Chin KV, *et al*. Regulation of mdr RNA levels in response to cyto toxic drugs in rodent cells. Cell Growth Differ 1990;1:361–365. [PubMed: 1703776]
41.Karssen AM, *et al*. Multidrug resistance P-glycoprotein hampers the access of cortisol but not of corticosterone to mouse and hu man brain. Endocrinology 2001;142:2686–2694. [PubMed: 11356720]
42.Pariante CM. The role of multi-drug resistance p-glycoprotein in glucocorticoid function: studies in animals and relevance in hu
43.Pariante CM, *et al*. Antidepressant fluoxetine enhances glucocorti coid receptor function in vitro by modulating membrane steroid transporters. Br J Pharmacol 2003;139:1111–1118. [PubMed: 12871829]
44.Lacroix A. Glucocorticoid effects on the nervous system and be haviour. UptoDate 2020
45.Chapman KE, Seckl JR. 11beta-HSD1, inflammation, metabolic disease and age-related cognitive (dys)function. Neurochem Res 2008;33:624–636. [PubMed: 17963039]
46.Revollo JR, Cidlowski JA. Mechanisms generating diversity in glucocorticoid receptor signaling. Ann N Y Acad Sci. 2009 Gluco corticoids and Mood: Clinical Manifestations, Risk Factors, and Molecular Mechanisms. In press.
47.Manenchijn L, *et al*. Clinical features associated with glucocorti coid receptor polymorphisms: an overview. Ann N Y Acad Sci. 2009 Glucocorticoids and Mood: Clinical Manifestations, Risk Factors, and Molecular Mechanisms. In Press
48.Spijker AT, Van Rossum EFC. Glucocorticoid receptor polymor phisms in major depression: focus on glucocorticoid sensitivity and neurocognitive functioning. Ann N Y Acad Sci. 2009 Glucocor ticoids and Mood: Clinical Manifestations, Risk Factors, and Mo lecular Mechanisms. In press.
49.van West D, *et al*. Glucocorticoid receptor gene-based SNP analysis in patients with recurrent major depression. Neuropsycho pharmacology 2006;31:620–627. [PubMed: 16192984]
50.Vandevyver S, Dejager L, Libert C. On the trail of the gluco corticoid receptor: into the nucleus and back. Traffic. (2011) 13:364–74. doi: 10.1111/j.1600-0854.2011.01288.x
51.Holaska JM, Black BE, Love DC, Hanover JA, Leszyk J, Paschal BM. Calreticulin is a receptor for nuclear export. J Cell Biol. (2001) 152:127– 40. doi: 10.1083/jcb.152.1.127
52.Holaska JM, Black BE, Rastinejad F, Paschal BM. Ca2+-depen dent nuclear export mediated by calreticulin. Mol Cell Biol. (2002) 22:6286– 97. doi: 10.1128/MCB.22.17.6286-6297.2002
53.Silverman MN, Sternberg EM. Neuroendocrine-immune inter

actions in rheumatoid arthritis: mechanisms of glucocorticoid resis tance. Neuroimmunology 2008;15:19–28.
54.Tait AS, Butts CL, Sternberg EM. The role of glucocorticoids and progestins in inflammatory, autoimmune, and infectious disease. J Leukoc Biol 2008;84:924–931. [PubMed: 18664528]
55.Colli LM, et al. Interindividual glucocorticoid sensitivity in young healthy subjects: the role of glucocorticoid receptor α and beta isoforms ratio. Horm Metab Res 2007;39:425–429. [PubMed: 17578759]
56.Tliba O, Cidlowski JA, Amrani Y. CD38 expression is insensitive to steroid action in cells treated with tumor necrosis factor-α and interferon-gamma by a mechanism involving the upregulation of the glucocorticoid receptor beta isoform. Mol Pharmacol 2006;69:588–596. [PubMed: 16291871]
57.Derijk RH, *et al*. A human glucocorticoid receptor gene variant that increases the stability of the glucocorticoid receptor beta-iso form mRNA is associated with rheumatoid arthritis. J Rheumatol 2001;28:2383–2388. [PubMed: 11708406]
58.Lee YM, *et al*. A mutation of the glucocorticoid receptor gene in patients with systemic lupus erythematosus. Tohoku J Exp Med 2004;203:69–76. [PubMed: 15212141]
59.Duma D, Jewell CM, Cidlowski JA. Multiple glucocorticoid receptor isoforms and mechanisms of post-translational modifica tion. J Steroid Biochem Mol Biol 2006;102:11–21. [PubMed: 17070034]
60.Joels M, *et al*. The coming out of the brain mineralocorticoid recep tor. Trends Neurosci 2008;31:1– 7. [PubMed: 18063498]
61.Chang TT, Yen YC. Cytokines and Major Psychiatric Disorders. Taiwanese Journal of Psychiatry Vol.24 No.4 2010
62.Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biol Psychiatry. 2013;73:1133–1141.
63.Popoli M, Yan Z, McEwen BS, Sanacora G. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. Nature. Jan, 2012; 13:22-37.
64.Krystal JH, State MW. Psychiatric Disorders: Diagnosis to Thera py. Cell. Author manuscript;PMC March 27 2015.
65.Juurlink BH, Schousboe A, Jørgensen OS, Hertz L. Induction by hydrocortisone of glutamine synthetase in mouse primary astrocyte cultures. J Neurochem 1981; 36:136.
mans. Eur J Pharmacol 2008;583:263–271. [PubMed: 18275949]
66.Hallermayer K, Harmening C, Hamprecht B. Cellular localization and regulation of glutamine synthetase in primary cultures of brain cells from newborn mice. J Neurochem 1981; 37:43.
67.Patel AJ, Hunt A. Observations on cell growth and regulation of glutamine synthetase by dexamethasone in primary cultures of forebrain and cerebellar astrocytes. Brain Res 1985; 350:175.
68.Wolkowitz OM, Rubinow D, Doran AR, Breier A, Berrettini WH, Kling MA (1990) Prednisone effects on neurochemistry and behaviour. Preliminary findings. Arch Gen Psychiatry 47: 963-968
69.Brown ES, Sayeda N, Choic C, Tustisond N, Robertsd J, Yassad MA, Van Enkevorta E, Nakamuraa A, Ivlevaa EI, Sunderajana P, Khanb DA, Vazquez M, McEwen B, Kulikovaa A, Frola AB, Holmesa T (2019) A randomized, double-blind, placebo-controlled trial of lamotrigine for prescription corticosteroid efects on the hu man hippocampus. Eur Neuropsychopharmacol 29:376–383.
70.Mirescu C, Peters JD, Noiman L, Gould E. Sleep deprivation inhibits adult neurogenesis in the hippocampus by elevating glu cocorticoids. Proc Natl Acad Sci U S A 2006; 103:19170.Hall RC, Popkin MK, Stickney SK, Gardner ER. Presentation of the steroid psychoses. J. Nerv. Ment. Dis. 1979; 167: 229–236.
71.Sanacora G, Mason GF, Krystal JH. Impairment of GABAergic transmission in depression: new insights from neuroimaging stud ies. Crit Rev Neurobiol. 2000;14:23–45.
72.Duman RS, Monteggia LM: A neurotrophic model for stressrelat ed mood disorders. Biol Psychiatry 2006; 59:1116–1127
73.Sapolsky RM. Glucocorticoids and hippocampal atrophy in neu ropsychiatric disorders. Arch Gen Psychiatry 2000; 57:925. 24.
74.Merke DP, Giedd JN, Keil MF, et al. Children experience cognitive decline despite reversal of brain atrophy one year after resolution of Cushing syndrome. J Clin Endocrinol Metab 2005; 90:2531.
75.Momose KJ, Kjellberg RN, Kliman B. High incidence of cortical atrophy of the cerebral and cerebellar hemispheres in Cushing's disease. Radiology 1971; 99:341.
76.Trethowan WH, Cobb S. Neuropsychiatric aspects of Cushing's syndrome. AMA Arch Neurol Psychiatry 1952; 67:283.
77.Cope O, Raker JW. Cushing's disease: the surgical experience in the care of 46 cases. N Engl J Med 1955; 253:119.
78.Bourdeau I, Bard C, Noël B, et al. Loss of brain volume in endoge nous Cushing's syndrome and its reversibility after correction of hypercortisolism. J Clin Endocrinol Metab 2002; 87:1949. Boele FW, Rooney AG, Grant R, Klein M. Psychiatric symptoms in gli oma patients: from diagnosis to management. Neuropsychiatric Disease and Treatment 2015;11:1413-1420
79.Bauduin SEEC, van der Wee NJA, van der Werff SJA. Structural brain abnormalities in Cushing's syndrome. Curr Opin Endocrinol Diabetes Obes 2018; 25:285.
80.Starkman MN, Gebarski SS, Berent S, Schteingart DE. Hippo campal formation volume, memory dysfunction, and cortisol lev els in patients with Cushing's syndrome. Biol Psychiatry 1992; 32:756.
81.Burkhardt T, Lüdecke D, Spies L, et al. Hippocampal and cerebel lar atrophy in patients with Cushing's disease. Neurosurg Focus 2015; 39:E5.
82.de Kloet ER, Joëls M, Holsboer F: Stress and the brain: from ad aptation to disease. Nat Rev Neurosci 2005; 6:463–475
83.Juruena MF, Cleare AJ, Pariante CM. The hypothalamic pituitary adrenal axis, glucocorticoid receptor function and relevance to depression. Rev Bras Psiquiatr 2004; 26:189-201. [PubMed: 15645065]
84.Chrousos GP, Kino T. Glucocorticoid action networks and complex psychiatric and/or somatic disorders. Stress 2007; 10:213-219 [PubMed: 17514590]
85.Holsboer F, Ising M. Central CRH System in depression and anxiety-evidence from clinical studies with CRH1 receptor antago nists. Eur J Pharmacol 2008; 583:350-357. [PubMed: 18272149]
86.Weber B, *et al*. Increased diurnal plasma concentrations of cortisone in depressed patients. J Clin Endocrinol Metab 2000;85:1133–1136. [PubMed: 10720051]
87.Silverman MN, et al. Immune modulation of the hypothalamic-pi tuitary-adrenal (HPA) axis during viral infection. Viral Immunol 2005;18:41–78. [PubMed: 15802953]
88.Sternberg EM. Neural regulation of innate immunity: a coordi nated nonspecific host response to pathogens. Nat Rev Immunol 2006;6:318–328. [PubMed: 16557263]
89.Marques-Deak A, Cizza G, Sternberg E. Brain-immune interac tions and disease susceptibility. Mol Psychiatry 2005;10:239–250. [PubMed: 15685252]
90.Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Ann N Y Acad Sci 2004;1024:138–146. [PubMed: 15265778]
91.Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun 2007;21:9–19. [PubMed: 17070667]
92.Maes M, Bosmans E, Calabrese J, *et al*.: Interleukin2 and interl eukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. J Psychiatr Res 1995; 29: 141-52
93.Pike JL, Irwin MR: Dissociation of infl ammatory markers and

DOI: 10.36838/v4i5.4

natural killer cell activity in major depressive disorder. Brain Behav Immun 2006; 20: 169-74.
94.Mesquita AR, Correia-Neves M, Roque S, *et al*.: IL10 modulates depressive-like behavior. Psychiatr Res 2008; 43: 89-97.
95.Dhabhar FS, Burke HM, Epel ES, *et a*l.: Low serum IL-10 con centrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. J Psychiatr Res 2009; 43: 962-9
96.Kubera M, Maes M: Serotonin-immune interactions in major depression In: Patterson, Kordon and Christen, Editors, Neuro-im mune Interactions in Neurologic and Psychiatric Disorders. Berlin: Springer-Verlag. 2000: 79-87.
97.Kenis G, Mase M: Effects of antidepressants on the production of cytokines. Neuropsychopharmacol 2002; 5: 401-12.
98.Pestka S, Krause CD, Sarkar D, *et al*.: Interlukin-10 and related cytokines and receptors. Ann Rev Immunol 2004; 22: 24-31.
99.Warrington TP, Bostwick JM: Psychiatric Adverse Effects of Cor ticosteroids. Mayo Clin Proc. 2006;81(10):1361-1367.
100.Fricchione G, Ayyala M, Holmes VF. Steroid withdrawal psychi atric syndrome. Ann Clin Psychiatry. 1989;1:99-108.
101.Dixon RB, Christy NP. On the various forms of corticosteroid withdrawal syndrome. Am J Med. 1980;68:224-230.
102.Kemp K, Lion JR, Magram G. Lithium in the treatment of a manic patient with multiple sclerosis: a case report. Dis Nerv Syst. 1977;38:210–211.
103.Terao T, Yoshimura R, Shiratuchi T, et al. Effects of lithium on steroid-induced depression. Biol Psychiatry. 1997;41:1225–1226.
104.The Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. Clin Pharma col Ther. 1972;13:694–698.
105.Hall RCW, Popkin MK, Stickney RN, et al. Presentation of the steroid psychosis. J Nerv Ment Dis. 1979;167:229–236.
106.Blazer DG, Petrie WM, Wilson WP. Affective psychosis follow ing renal transplant. Dis Nerv Syst. 1976;37:663–667.
107.Silva RG, Tolstunov L. Steroid-induced psychosis: report of a case. J Oral Maxillofacial Surg. 1995;53:183–186.
108.Baloch N. Steroid psychosis: a case report. Br J Psychiatry. 1974;124:545–546.
109.Brown ES, Stuard G, Liggin JD, Hukovic N, Frol A, Dhanani N, Khan DA, Jeffress J, Larkin GL, McEwen BS, Rosenblatt R, Mageto Y, Hanczyc M, Cullum CM: Effect of phenytoin on mood and declarative memory during prescription corticosteroid therapy. Biol Psychiatry 2005; 57:543–548
110.Roxanas MG, Hunt GE: Rapid reversal of corticosteroid-in duced mania with sodium valproate: a case series of 20 patients. Psychosomatics 2012; 53:575–581
111.Black AC. Biochemical mechanisms of steroid-induced psycho sis. N. Y. State J. Med. 1982; 82: 1024.
112.Gilad GM, Rabey JM, Gilad VH. Presynaptic effects of glu-cocorticoids on dopaminergic and cholinergic synaptosomes. Implications for rapid endocrine-neural interactions in stress. Life Sci. 1987; 40: 2401–2408.
113.Beshay H, Pumariega AJ. Sertraline treatment of mood disorder associated with prednisone: a case report. J. Child Adolesc. Psycho pharmacol. 1998; 8: 187–193.
114.Handley R, Mondelli V, Zelaya F, Marques T, Taylor H, Reinders AATS, Chaddock C, McQueen G, Hubbard K, Papadopoulos A, Williams S, McGuire P, Pariante C, Dazzan P (2016) Efects of antipsychotics on cortisol, interleukin-6 and hippocampal perfu sion in healthy volunteers. Schizophr Res 174(1–3):99–105. https ://doi.org/10.1016/j.schres.2016.03.039
115.Desai S, Khanani S, Shad MU, Brown ES: Attenuation of amyg dala atrophy with lamotrigine in patients receiving corticosteroid therapy. J Clin Psychopharmacol 2009; 29:284–287
116.Brown ES, Wolfshohl J, Shad MU, Vazquez M, Osuji IJ: Attenu ation of the effects of corticosteroids on declarative memory with lamotrigine. Neuropsychopharmacology 2008; 33:2376– 2383
117.Brown ES, Vazquez M, Nakamura A: Randomized, placebocon trolled, crossover trial of memantine for cognitive changes with corticosteroid therapy. Biol Psychiatry 2008; 64:727–729
118.de Quervain DJF, Aerni A, Roozendaal B: Preventive effect of beta-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. Am J Psychiatry 2007; 164:967–969
119.Carta MG, Moro MF, Lorefice L, Trincas G, Cocco E, Giudice ED, Fenu G, Colom F, Marrosu MG: The risk of bipolar disorders in multiple sclerosis. J Affect Disord 2014; 155:255–260
120.Thielscher C, Thielscher S, Kostev K: The risk of developing de pression when suffering from neurological diseases. Ger Med Sci 2013; 11:Doc02
121.Yang J, Sun LH, Yang W ,Cui R.J. Bai SK. The Role of BDNF in the Neuroimmune Axis Regulation of Mood Disorders. frontiers in Neurology. June,2019;10:Article 515.
122.Samuel S, Nguyen T, Choi HA. Pharmacologic Characteristics of Corticosteroids. J Neurocrit Care 2017;10(2):53-59
123.Letters to the Editor. Am J Psychiatry June 1999; 156:6
124.Holsboer F. The corticosteroid receptor hypothesis of depres sion. Neuropsychopharmacology 2000;23:477–501. [PubMed: 11027914]
125.Nemeroff CB. The corticotropin-releasing factor (CRF) hy pothesis of depression: new findings and new directions. Mol Psy chiatry 1996;1:336–342. [PubMed: 9118360]
126.Bhangle SD, Kramer N, Rosenstein ED: Corticosteroid-induced neuropsychiatric disorders: review and contrast with neuropsychi atric lupus. Rheumatol Int 2013; 33:1923–1932
127.Fardet L, Flahault A, Kettaneh A, Tiev KP, Généreau T, Tolédano C, Lebbé C, Cabane J: Corticosteroid-induced clinical adverse events: frequency, risk factors, and patient's opinion. Br J Dermatol 2007; 157:142–148
128.Fardet L, Petersen I, Nazareth I: Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in pri mary care. Am J Psychiatry 2012; 169:491–497
129.Brown ES, Suppes T, Khan DA, Carmody TJ 3rd: Mood changes during prednisone bursts in outpatients with asthma. J Clin Psy chopharmacol 2002; 22:55–61
130.Lieb K, Engelbrecht MA, Gut O, Fiebich BL, Bauer J, Janssen G, Schaefer M: Cognitive impairment in patients with chronic hepa titis treated with interferon α (IFNα): results from a prospective study. Eur Psychiatry 2006; 21:204–210
131.Gift AG, Wood RM, Cahill CA: Depression, somatization, and steroid use in chronic obstructive pulmonary disease. Int J Nurs Stud 1989; 26:281–286
132.Wolkowitz OM, Burke H, Epel ES, Reus VI: Glucocorticoids: mood, memory, and mechanisms. Ann N Y Acad Sci 2009; 1179:19– 40
133.Bender BG, Lerner JA, Kollasch E: Mood and memory changes in asthmatic children receiving corticosteroids. J Am Acad Child Adolesc Psychiatry 1988; 27:720–725
134.Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ: Cortisol levels during human aging predict hippocampal atrophy and mem ory deficits. Nat Neurosci 1998; 1:69–73
135.Aulakh R, Singh S: Strategies for minimizing corticosteroid tox icity: a review. Indian J Pediatr 2008; 75:1067–1073

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