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Impact of Frequent Steroid Prescription

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A B S T R A C T
Corticosteroids are a class of steroid hormones released by the adrenal cortex, which includes glucocorticoids and mineralocorticoids. However, the term "corticosteroids" is generally used to refer to glucocorticoids. Named for their effect in carbohydrate metabolism, glucocorticoids regulate diverse cellular functions including development, homeostasis, metabolism, cognition and inflammation[2]. Due to their profound immunomodulatory actions, glucocorticoids are one of the most widely prescribed drugs in the world and the worldwide market for glucocorticoids is estimated to be worth more than USD 10 billion per year. Glucocorticoids have become a clinical mainstay for the treatment of numerous inflammatory and autoimmune diseases, such as asthma, allergy, septic shock rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. These side effects include osteoporosis, skin atrophy, diabetes, abdominal obesity, glaucoma, cataracts, avascular necrosis and infection, growth retardation, and hypertension. Understanding the molecular mechanisms underlying the physiological and pharmacological actions of glucocorticoids is of great importance as it may aid in developing synthetic glucocorticoids with increased tissue selectivity, which can thereby minimize the side effects by dissociating the desired anti-inflammatory functions from undesirable adverse outcomes.
Keywords: Glucocorticoids, mineralocorticoids. abdominal obesity, glaucoma, cataracts, side effects.

A R T I C L E I N F O

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1. Introduction

Steroid**,** any of a class of natural or synthetic organic compounds characterized by a molecular structure of 17 carbon atoms arranged in four rings. Steroids are important in biology, chemistry, and medicine. The steroid group includes all the sex hormones, adrenal cortical hormones, bile acids, and sterols of vertebrates, as well as the molting hormones of insects and many other physiologically active substances of animals and plants. Among the synthetic steroids of therapeutic value are a large number of anti-inflammatory agents, anabolic (growth-stimulating) agents, and oral contraceptives. Different categories of steroids are frequently

distinguished from each other by names that relate to their biological source e.g., phytosterols (found in plants), adrenal steroids, and bile acids or to some important physiological function—e.g., progesterones (promoting gestation), androgens (favouring development of masculine characteristics), and cardiotonic steroids (facilitating proper heart function). Steroids vary from one another in the nature of attached groups, the position of the groups, and the configuration of the steroid nucleus (or gonane). Small modifications in the molecular structures of steroids can produce remarkable differences in their biological activities. Corticosteroids, often known as steroids, are an anti-inflammatory medicine prescribed for a wide range of conditions[1-4].

Corticosteroids are available in different forms, including:

- tablets (oral steroids)
- injections – which can be into blood vessels, joints or muscles
- inhalers – such as mouth or nasal sprays
- lotions, gels or creams (topical steroids)

Corticosteroids uses:

They are used to treat conditions such as:

- asthma
- allergic rhinitis and hay fever
- urticaria (hives)
- atopic eczema
- chronic obstructive pulmonary disease (COPD)
- painful and inflamed joints, muscles and tendons
- lupus
- inflammatory bowel disease (IBD) – including Crohn's disease and ulcerative colitis
- giant cell arteritis and polymyalgia rheumatica
- multiple sclerosis (MS)

History of steroids

The first therapeutic use of steroids occurred in the 18th century when English physician William Withering used digitalis, a compound extracted from the leaves of the common foxglove (*Digitalis purpurea*), to treat edema. Studies of steroids commenced in the early 19th century with investigations of the unsaponifiable (i.e., remaining undissolved after heating with excess of alkali) material, largely cholesterol, of animal fat and gallstones and of acids obtainable from bile. This early work, with which many of the noted chemists of the time were associated, led to the isolation of cholesterol and some bile acids in reasonable purity and established some significant features of their chemistry[5-9].

Indications

Corticosteroids are hormone mediators produced by the cortex of adrenal glands that are further categorized into glucocorticoids (major glucocorticoid produced by the body is cortisol), mineralocorticoids (major mineralocorticoid produced in the body is aldosterone), and androgenic sex hormones. Glucocorticoids (GCs) are a group of drugs structurally and pharmacologically similar to the endogenous hormone cortisol with various functions like anti-inflammatory, immunosuppressive, anti-proliferative, and vaso-constrictive effects.

As a Replacement Therapy

- Adrenocortical insufficiency (Addison disease)
- Congenital adrenal hyperplasia (CAH)

Systemic Symptomatic Treatment

Acute

- Allergic reactions and anaphylactic shock (vasoconstrictive effects)
- Asthma (bronchodilatory effects)
- Antiemetic treatment, for example, nausea due to chemotherapy)
- Toxic pulmonary edema
- Acute exacerbation of autoimmune diseases such as multiple sclerosis, vitiligo, uveitis, rheumatoid arthritis, SLE, etc.
- Acute exacerbation of chronic obstructive pulmonary disease (COPD)
- Cerebral edema: Recommended only in specific conditions like elevated intracranial pressure due to the neoplasm or central nervous system (CNS) infection; generally avoided in moderate to severe brain injury

Long-Term

- Chronic inflammatory diseases (asthma, chronic obstructive pulmonary disease, inflammatory bowel disease)
- Rheumatic diseases (sarcoidosis, Sjogren syndrome, SLE)
- Graves' ophthalmopathy
- Local symptomatic treatment: anterior uveitis, steroid-responsive dermatoses (SRD), tenosynovitis, and osteoarthritis or juvenile idiopathic arthritis[10-15].

Prophylactic

- Organ transplant (to prevent rejection due to their immunosuppressive action)
- Preterm delivery (to allow fetal lung maturity)

Mechanism of Action

Anti-Inflammatory and Immunosuppressive Effects

The anti-inflammatory and immunosuppressive effects of glucocorticoids are dose-dependent, with immunosuppressive effects seen mostly at higher doses. The pharmacological anti-inflammatory and immunosuppressive effects of glucocorticoids are extensive and can occur via genomic or non-genomic mechanisms. Most effects of glucocorticoids are via the genomic mechanisms, which takes time, while immediate effects via the non-genomic mechanisms can occur with high doses of glucocorticoids (such as pulse therapy). Clinically, it is not possible to separate these effects.

Genomic Mechanisms

Being small, lipophilic substances, glucocorticoids readily pass the cell membrane by diffusion and enter the cytoplasm of the target cells, where most of their action is mediated by binding to the intra-cytoplasmic

glucocorticoid receptors. Glucocorticoid receptors have two isoforms, α, and β. Glucocorticoids bind to the α-isoform only. Glucocorticoid resistance in some patients has been partly attributed to higher levels of the β-isoform in these patients.[2] The binding of the glucocorticoid to the glucocorticoid receptor results in the shedding of heat-shock proteins, which are otherwise bound to the glucocorticoid receptor, which results in the formation of the activated glucocorticoid receptor-glucocorticoid complex, which easily translocates to the nucleus. In the nucleus of the target cells, this complex reversibly binds to several specific DNA sites resulting in stimulation (transactivation) and suppression (transrepression) of a large variety of gene transcription[16-19].

Non-Genomic Mechanisms

The immediate effects of high dose-glucocorticoids are mediated via non-genomic mechanisms. At high doses, glucocorticoids bind the membrane-associated glucocorticoid receptors on target cells such as T-lymphocytes, resulting in impairment of receptor signaling and immune response of the T lymphocytes. High-dose glucocorticoids also interact with the cycling of calcium and sodium across the cell membrane resulting in a rapid decrease in inflammation.

By altering the cytokine production via the genomic and non-genomic mechanisms, glucocorticoids lead to suppression of the immune system and decreased inflammation. They target a wide variety of cells, including T-lymphocytes, macrophages, fibroblasts, neutrophils, eosinophils, and basophils. Notably, glucocorticoids have almost no effect on B-cell function and immunoglobulin production. The downstream effects of glucocorticoids are summarized below:

- Inhibition of neutrophil adhesion to endothelial cells and demargination of neutrophils from the marginal pool of blood vessels causing neutrophilic leukocytosis
- A decrease in the number of lymphocytes, macrophages, monocytes, eosinophils, and basophils (decreased myelopoiesis and release from bone marrow, and increased apoptosis)
- Decreased proliferation of fibroblasts
- Decreased MHC-Class II and Fc receptor expression on macrophages and monocytes
- Decreased phagocytosis and antigen presentation by macrophages
- Decreased cytokine production by macrophages and lymphocytes
- Decreased proliferation of fibroblasts.
- Reduction in the formation of arachidonic acid derivatives by the promotion of synthesis of lipocortin-A that inhibits phospholipase A2
- Inhibition of metalloproteinases collagenase and stromelysin, which are otherwise responsible for cartilage degradation

Mineral corticoid Effects

Glucocorticoids bind to mineralocorticoid receptors (MRs) and produce their mineralocorticoid effect (i.e., increasing sodium and decreasing potassium), but only when used at the high dose and for an extended period.

Administration

Several preparations of glucocorticoids are available, each with varying efficacy. Dexamethasone and betamethasone are long-acting with the highest glucocorticoid efficacy with a biological half-life of 36 to 54 hours. Cortisone and cortisol are short-acting with a biological half-life of under 12 hours and are not frequently used.

Intravenous Administration

Parenteral intravenous administration of high doses of glucocorticoids may be warranted in emergencies, such as septic shock, COPD exacerbation, and severe acute asthma[17-19].

Oral Administration

Oral preparations are usually useful in both acute and chronic indications. For acute exacerbations of underlying chronic illness (such as asthma, COPD, gout, pseudogout, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), etc.), short duration of moderate to high doses of oral corticosteroids is usually efficacious in treating the flare. Tapering dose packs starting at high doses and tapering daily over 7 to 9 days are commercially available and can be used in these situations as well. Long-term oral corticosteroid therapy may be necessary for chronic illnesses such as polymyalgia rheumatica, SLE, RA, vasculitis, myositis, IgG4-related disease, chronic myelogenous leukemia (CML), lymphoma, leukemia, multiple sclerosis, organ transplantation, etc.

Local Administration

Glucocorticoid administration can be via several non-systemic routes, including intra-articular joint injections for joint inflammation, inhalational for asthma, topical for dermatological problems, ocular drops for eye conditions, and intra-nasal for seasonal rhinitis[20-25].

Adverse Effects

Factors Influencing the Adverse Effects of Glucocorticoids

Adverse effects of corticosteroids are both dose and time-dependent. Some adverse effects follow a linear dose-response pattern where the incidence increases with an increase in the dose (ecchymosis, cushingoid features, parchment-like skin, leg edema, and sleep disturbance). Other adverse effects may follow a threshold dose-response pattern with an elevated frequency of events beyond a specific threshold value (weight gain and epistaxis at prednisone dose greater than 5 mg daily, glaucoma, depression, hypertension at prednisone dose greater than 7.5 mg daily, etc.).

Musculoskeletal Adverse Effects

Glucocorticoids induced Osteoporosis is one of the well-known and devastating adverse effects of long-term use of glucocorticoids. Up to 40% of patients on long-term glucocorticoids develop bone loss leading to fractures.

Several mechanisms play a role, including osteoclast activation by promoting RANK-ligand as well as a decrease in function and number of osteoblasts and osteocytes. The trabecular bone is initially affected, with cortical bone loss seen with longer-term use. The loss of trabecular bone can occur within the first 6 to 12 months of therapy[26-27].

Steroid-induced myopathy, which is a reversible painless myopathy and is a direct result of muscle breakdown, can occur in both the upper and lower extremities, usually with high-dose long-term use of glucocorticoids. Muscle enzymes (CK and Aldolase) are typically normal, and findings on electromyography are non-specific. Muscle biopsy reveals Type-II fiber atrophy without inflammation. Withdrawal of glucocorticoids and exercises usually results in the resolution of myopathy. "Critical illness myopathy" may also develop in patients admitted in the intensive care unit (ICU) requiring large doses of IV glucocorticoids and neuromuscular blocking agents.

Osteonecrosis can be seen especially with long-term use of prednisone more than 20 mg daily. Patients with SLE and children are at higher risk. Hips and knees are the most commonly involved joints with less common involvement of shoulders and ankles. Pain is the initial feature, which may eventually become severe and debilitating.

Metabolic and Endocrine Adverse Effects

Systemic glucocorticoids cause a dose-dependent increase in fasting glucose levels and a more significant increase in postprandial values in patients without preexisting diabetes mellitus, but the development of de novo diabetes in a patient with initially normal glucose tolerance is uncommon. The development of cushingoid features (redistribution of body fat with truncal obesity, buffalo hump, and moon face) and weight gain are dose and duration-dependent and can develop early. Cushingoid features showed a linear increase in frequency with dosing. Glucocorticoid therapy is the most common cause of Cushing syndrome.

Administration of glucocorticoids can suppress the hypothalamic-pituitary-adrenal (HPA) axis decreasing corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, and endogenous cortisol. Prolonged ACTH suppression cause atrophy of adrenal glands, and abrupt cessation or rapid withdrawal of Glucocorticoids in such patients may cause symptoms of adrenal insufficiency. The clinical presentation of adrenal suppression is variable.

Infections

Moderate to high dose use of glucocorticoids poses a significant risk of infections, including common mild infections as well as serious life-threatening infections. There is a linear increase in the risk with dose and duration of therapy, especially with common bacterial, viral, and fungal pathogens. Concomitant use of other immunosuppressive agents and the elderly age further increases the risk of infections.

Cardiovascular Adverse Effects

Mineralocorticoid effects, especially as seen with cortisol and cortisone, can lead to fluid retention, edema, weight gain, hypertension, and arrhythmias by increasing renal excretion of potassium, calcium, and phosphate. Hypertension usually occurs with higher doses only.

Dermatologic Adverse Effects

Several cutaneous adverse effects can occur even at a low dose use of glucocorticoids, although the risk increases linearly with the increasing dose and duration of glucocorticoid therapy. Although cutaneous adverse effects appear to be clinically significant by physicians, they are usually of most concern to the patients. These adverse effects include ecchymosis, skin thinning and atrophy, acne, mild hirsutism, facial erythema, stria, impaired wound healing, thinning of hair, and perioral dermatitis.

Ophthalmologic Adverse Effects

The risk of cataracts is significantly high in patients taking prednisone more than 10 mg daily for more than one year, with a dose-dependence in a linear fashion. However, an increased risk of cataracts has been reported even with low-dose glucocorticoids. Cataracts are usually bilateral and slowly progressing. Increased intraocular pressure, especially in patients with a family history of open-angle glaucoma, is seen in patients receiving intraocular glucocorticoids and high dose systemic glucocorticoids.

Gastrointestinal (GI) Adverse Effects

Glucocorticoids increase the risk of adverse GI effects, such as gastritis, gastric ulcer formation, and GI bleeding.

Neuropsychiatric Adverse Effects

Disturbances in sleep are reported, especially with split doses that may interfere with the normal pattern of diurnal cortisol production. Akathisia (motor restlessness) is a common glucocorticoid side effect. The risk of developing a given neuropsychiatric disorder following glucocorticoid therapy may increase among patients with a history of the condition. Rare cases of pseudotumor cerebri have also correlated with glucocorticoid use.

Contraindications

General contraindications include hypersensitivity.

Systemic

- Systemic fungal infections
- Intrathecal administration
- Cerebral malaria
- Concomitant live or live attenuated virus vaccination (if using glucocorticoids in immunosuppressive doses)
- Idiopathic thrombocytopenic purpura (IM administration)
- Use in premature infants (formulations containing benzyl alcohol)

Topical

- Dermatological: Bacterial, viral, or fungal infection of the mouth or throat (triamcinolone)
- Ophthalmic: Acute untreated purulent ocular infections, fungal or mycobacterial ocular infections, viral conjunctivitis, or keratitis

Clinicians can administer live virus vaccines to patients who are on:

- Prednisone or it
- s equivalent in doses of less than 20 mg per day for 14 days or less
- Glucocorticoids used for long-term physiologic replacement
- Glucocorticoids administered topically, by aerosol, or by intra-articular or bursal injection, provided that there is no clinical or laboratory evidence of immunosuppression

Monitoring

Baseline Assessment and Monitoring

Preexisting conditions that should be assessed for and treated when starting glucocorticoids include:

- Diabetes mellitus
- Poorly controlled hypertension
- Heart failure and peripheral edema
- Cataract or glaucoma
- Peptic ulcer disease
- Presence of infection
- Low bone density or osteoporosis
- Psychiatric illness

Subsequent Monitoring

Assessment of Bone Health

American College of Rheumatology has published specific guidelines addressing this issue to help prevent and manage GiOp.

- All adults receiving prednisone 2.5 mg or more daily for more than three months shall be encouraged to optimize calcium and vitamin D intake, and shall be counseled to quit smoking, have a balanced diet and be engaged in regular weight-bearing exercises, and limit alcohol intake to 1 to 2 alcoholic beverages in a day.
- Clinical fracture risk reassessment shall be performed at baseline and every 12 months in patients receiving long-term glucocorticoids.
- Bone mineral density (BMD) measurement via DEXA scan shall be performed ideally before or within six months after the initiation of glucocorticoid therapy in all adults 40 years of age or more, and in adults younger than 40 years of age if there is a history of osteoporotic fractures or other risk factors for osteoporosis.
- In adults 40 years of age or more, the 10-year fracture risk assessment is necessary using the FRAX tool (a diagnostic tool that incorporates clinical factors and bone mineral density at the femoral neck).
- Based on the above data, in addition to the dose and duration of glucocorticoid therapy, patients fall into three fracture risk categories: low risk, moderate risk, and high risk. Their fracture risk category shall dictate further management.
- Bisphosphonates, teriparatide, or denosumab shall be recommended in patients less than 40 years of age but in the moderate or high fracture risk category.
- Bisphosphonates, teriparatide, denosumab, or raloxifene shall be recommended in patients 40 years of age or more in the moderate or high fracture risk category.
- Oral bisphosphonates are preferred in all these patients.
- Lateral spine X-ray shall be considered in adults 65 years of age or older to evaluate for vertebral fractures.
- Consider referral to endocrinologist/ rheumatologist if fracture risk is high and/or BMD is declining.

Assessment of Hypothalamic: Pituitary-Adrenal (HPA) Function

The HPA axis should undergo assessment if the patient has received systemic corticosteroids for more than two consecutive weeks or more than three cumulative weeks in the last six months or if the patient has persistent symptoms of adrenal suppression. Screening is by measuring early morning salivary cortisol after tapering off the dose of cortisol. If morning cortisol is normal, but the patient has symptoms of adrenal suppression, perform a low-dose ACTH stimulation test to confirm the diagnosis. Consider endocrinology referral for confirmation of diagnosis[27-29].

Assessment of Dyslipidemia and Cardiovascular Risk (Adults)

Lipid profile shall be monitored one month after glucocorticoid initiation and then every 6 to 12 months. Glycemic control requires assessment via screening for classic symptoms at every visit: polyuria, polydipsia, weight loss. Monitor glucose parameters for at least 48 hours after glucocorticoids initiation, then every 3 to 6 months for the first year and annually afterward. In children, an annual oral glucose tolerance test merits consideration if the child is obese or has risk factors for diabetes.

Assessment of Ophthalmological Complications

An annual ophthalmological examination shall be considered, especially for those with symptoms of cataracts, and early referral for intraocular pressure assessment should occur if there is a personal or family history of open-angle glaucoma, diabetes mellitus, or high myopia[30-31].

Prevention of Adverse Effects

Although some adverse effects of glucocorticoids are unavoidable, some can be prevented by:

- Use of the lowest dose of glucocorticoids for the shortest period needed to achieve the treatment goals
- Management of preexisting comorbid conditions
- Monitoring of patients under treatment for adverse effects

Withdrawal of Glucocorticoid Therapy

Abrupt cessation of chronic glucocorticoid therapy can be dangerous as there is a risk of HPA axis suppression. Withdrawal of glucocorticoid therapy needs tapering over the period. In general, patients who are given acute corticosteroid therapy for less than 14 to 21 days do not develop HPA axis suppression, and treatment can stop with no need for any tapering regime in them. If the therapy has been ongoing for greater than three weeks, tapering is needed (e.g., over two months), but there is no universally accepted optimal regimen.

Toxicity

Acute psychosis can develop in patients receiving high-dose glucocorticoids. Immediate cessation of the drug on the appearance of symptoms is the first step[32-35]. Although many drugs, including antipsychotics, antidepressants, benzodiazepines, and hydrocortisone, have been tried with variable success, currently, there is no consensus on the ideal therapeutic remedy to stop and reverse the corticosteroid-induced neuropsychiatric adverse effects in adults or children.

2. Conclusion

Corticosteroids, often known as steroids, are an anti-inflammatory medicine prescribed for a wide range of conditions. steroids have infiltrated nearly every branch of medicine and can be administered in nearly every route available. The effects of steroid use can vary widely, and the full spectrum of side effects can be present even in patients taking low dose of administration. The clinicians must be aware that the drug can possibly exacerbate a preexisting condition or present a new medical condition. The effective understanding of side effects of corticosteroids and correct dose of prescribing with correct disease indication could lower the future of corticosteroids drug harmful effects in practice.

3. References

[1] Xu J, Winkler J, Derendorf H. A pharmacokinetic/pharmacodynamic approach to predict total prednisolone concentrations in human plasma. *J Pharmacokinet Pharmacodyn*. 2007 Jun;34(3):355–372. Epub 2007 Feb 23.

[2] Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum*. 2006 Jun 15;55(3):420–426.

[3] Kenna HA, Poon AW, de los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry Clin Neurosci*. 2011 Oct;65(6):549–560.

[4] Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc*. 2006 Oct;81(10):1361–1367.

[5] Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. *Drug Saf*. 2000 Feb;22(2):111–122.

[6] Pereira RM, Carvalho JF, Canalis E. Glucocorticoid-induced osteoporosis in rheumatic diseases. *Clinics (Sao Paulo)* 2010;65(11):1197–1205.

[7] Lansang MC, Hustak LK. Glucocorticoid-induced diabetes and adrenal suppression: how to detect and manage them. *Cleve Clin J Med*. 2011 Nov;78(11):748–756.

[8] Benzon HT, Gissen AJ, Strichartz GR, Avram MJ, Covino BG. The effect of polyethylene glycol on mammalian nerve impulses. *Anesth Analg*. 1987 Jun; 66(6):553–559.

[9] Craig DB, Habib GG. Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol. *Anesth Analg*. 1977 Mar-Apr; 56(2):219–221.

[10] Ahadian FM, McGreevy K, Schulteis G. Lumbar transforaminal epidural dexamethasone: a prospective, randomized, double-blind, dose-response trial. *Reg Anesth Pain Med*. 2011 Nov-Dec;36(6):572–578.

[11] Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. *Pain Med*. 2006 May-Jun, 7(3):237–242.

[12] Somayaji HS, Saifuddin A, Casey AT, Briggs TW. Spinal cord infarction following therapeutic computed tomography-guided left L2 nerve root injection. *Spine (Phila Pa 1976)* 2005 Feb 15;30(4):E106–E108.

[13] McClain RW, Yentzer BA, Feldman SR. Comparison of skin concentrations following topical versus oral corticosteroid treatment: reconsidering the treatment of common inflammatory dermatoses. *J Drugs Dermatol*. 2009 Dec;8(12):1076–1079.

[14] Morley KW, Dinulos JG. Update on topical glucocorticoid use in children. *Curr Opin Pediatr*. 2012 Feb;24(1):121–128.

[15] Busse WW, Bleecker ER, Bateman ED, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. *Thorax*. 2012 Jan;67(1):35–41. Epub 2011 Aug 9.

[16] Doherty DE, Tashkin DP, Kerwin E, et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic

obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. *Int J Chron Obstruct Pulmon Dis*. 2012; 7:57–71. Epub 2012 Feb 3.

[17] Taplin CE, Cowell CT, Silink M, Ambler GR. Fludrocortisone therapy in cerebral salt wasting. *Pediatrics*. 2006 Dec;118(6):e1904–e1908.

[18] Freitas J, Santos R, Azevedo E, Costa O, Carvalho M, de Freitas AF. Clinical improvement in patients with orthostatic intolerance after treatment with bisoprolol and fludrocortisone. *Clin Auton Res*. 2000 Oct; 10(5):293–299.

[19] Wallner BP, Mattaliano RJ, Hession C, et al. Cloning and expression of human lipocortin, a phospholipase A2 inhibitor with potential anti-inflammatory activity. *Nature*. 1986 Mar 6-12; 320(6057):77–81.

[20] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med*. 2005 Oct 20; 353(16):1711–1723.

[21] Blackwell GJ, Carnuccio R, Di Rosa M, Flower RJ, Parente L, Persico P. Macrocortin: a polypeptide causing the anti-phospholipase effect of glucocorticoids. *Nature*. 1980 Sep 11; 287(5778): 147–149.

[22] Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003 Feb 20;348(8):727–734.

[23] Cao Y, Bender IK, Konstantinidis AK, Shin SC, Jewell CM, Cidlowski JA, et al. Glucocorticoid receptor translational isoforms underlie maturational stage-specific glucocorticoid sensitivities of dendritic cells in mice and humans. Blood. 2013;121:1553–62.

[24] Sinclair D, Webster MJ, Wong J, Weickert CS. Dynamic molecular and anatomical changes in the glucocorticoid receptor in human cortical development. Mol Psychiatry. 2011;16:504–15.

[25] 70. Sinclair D, Webster MJ, Fullerton JM, Weickert CS. Glucocorticoid receptor mRNA and protein isoform alterations in the orbitofrontal cortex in schizophrenia and bipolar disorder. BMC Psychiatry. 2012;12:84.

[26] Beck IM, Vanden Berghe W, Vermeulen L, Yamamoto KR, Haegeman G, De Bosscher K. Crosstalk in inflammation: the interplay of glucocorticoid receptor-based mechanisms and kinases and phosphatases. Endocr Rev. 2009;30:830–82.

[27] Wang Z, Frederick J, Garabedian MJ. Deciphering the phosphorylation “code” of the glucocorticoid receptor in vivo. J Biol Chem. 2002;277:26573–80.

[28] Avenant C, Ronacher K, Stubsrud E, Louw A, Hapgood JP. Role of ligand-dependent GR phosphorylation and half-life in determination of ligand-specific transcriptional activity. Mol Cell Endocrinol. 2010;327:72–88.

[29] Galliher-Beckley AJ, Williams JG, Collins JB, Cidlowski JA. Glycogen synthase kinase 3beta-mediated serine phosphorylation of the human glucocorticoid receptor redirects gene expression profiles. Mol Cell Biol. 2008;28:7309–22.

[30] Galliher-Beckley AJ, Williams JG, Cidlowski JA. Ligand-independent phosphorylation of the glucocorticoid receptor integrates cellular stress pathways with nuclear receptor signaling. Mol Cell Biol. 2011; 31:4663–75.

[31] Webster JC, Jewell CM, Bodwell JE, Munck A, Sar M, Cidlowski JA. Mouse glucocorticoid receptor phosphorylation status influences multiple functions of the receptor protein. J Biol Chem. 1997; 272:9287–93.

[32] Chen W, Dang T, Blind RD, Wang Z, Cavasotto CN, Hittelman AB, et al. Glucocorticoid receptor phosphorylation differentially affects target gene expression. Mol Endocrinol. 2008;22:1754–66.

[33] Deroo BJ, Rentsch C, Sampath S, Young J, DeFranco DB, Archer TK. Proteasomal inhibition enhances glucocorticoid receptor transactivation and alters its sub-nuclear trafficking. Mol Cell Biol. 2002; 22: 4113–23.

[34] Wallace AD, Cidlowski JA. Proteasome-mediated glucocorticoid receptor degradation restricts transcriptional signaling by glucocorticoids. J Biol Chem. 2001;276:42714–21.

[35] Wang X, DeFranco DB. Alternative effects of the ubiquitin-proteasome mediated by CHIP, an E3 ligase. Mol Endocrinol. 2005;19:1474–82.