Therapeutic uses of adrenal corticosteroids include:

1. Replacement therapy:

Primary adrenocortical insufficiency (Addison disease):

- Caused by adrenal cortex dysfunction. **Hydrocortisone** (identical to natural cortisol), is given to correct the deficiency. 2/3 of the normal daily dose of **hydrocortisone** is given in the morning and 1/3 is given in the afternoon (to mimic the daily circadian rhythm exhibited by cortisol).
- **Fludrocortisone**, (potent synthetic mineralocorticoid with some glucocorticoid activity), may also be given to raise the mineralocorticoid activity to normal levels.

b. Secondary or tertiary adrenocortical insufficiency:

- Caused by a defect in the production of CRH (from hypothalamus) or ACTH (from pituitary). **Hydrocortisone** is used for treatment of these deficiencies (**note**: synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids).

c. Congenital adrenal hyperplasia (CAH):

- Group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. This condition may lead to virilization in females due to overproduction of adrenal androgens.
- The choice of replacement hormone depends on the specific enzyme defect. The administration of corticosteroids suppresses the release of CRH and ACTH, thus it decreases production of adrenal androgens.

2. Diagnosis of Cushing syndrome:

- Cushing syndrome is caused by a hypersecretion of glucocorticoids due to excessive release of corticotropin by the anterior pituitary or an adrenal tumor.
- **Dexamethasone** suppression test is used to diagnose and differentiate the cause of Cushing syndrome.
- **Dexamethasone** suppresses cortisol release due to pituitary- dependent Cushing syndrome, but not suppress glucocorticoid released from adrenal tumors.

Note: Iatrogenic Cushing syndrome is caused by chronic treatment with high doses of glucocorticoid.

3. Relief of inflammatory symptoms & immunosuppression:

Glucocorticoids dramatically reduce the manifestations of inflammation (eg. rheumatoid and osteoarthritic inflammation as well as skin inflammatory conditions). The effect of glucocorticoids on the inflammatory process is the result of a number of actions, including:

a. Redistribution of leukocytes to other body compartment.
b. Increase the concentration of neutrophils.
c. Decrease the concentration of lymphocytes (T & B cells), basophils, eosinophils & monocytes.
d. Inhibit the responses of leukocytes & macrophages to mitogens & Ags.
e. The glucocorticoids central anti-inflammatory action is the inhibition of PGs & LTs production.
f. They also reduce histamine release from basophils & mast cells, thus diminishing the activation of the kinin system.

4. Treatment of allegies:

Symptoms of bronchial asthma, allergic rhinitis & drug, serum & transfusion allergic reactions can be treated with glucocorticoids.

Inhalation of beclomethasone, triamcinolones & others can minimize systemic effects.

5. Acceleration of lung maturation:

- Fetal cortisol is a regulator of lung maturation.
- A dose of beclomethasone is given I.M to the mother 48 hours prior to birth, followed by a 2nd dose 24 hours before delivery can be used to prevent the development of respiratory distress syndrome in premature infants.

Pharmacokinetics:

- All glucocorticoids can be administered orally (readily absorbed from GIT).
- Selected agents can also be given I.V, I.M, intra-articularly (into arthritic joints), topically or as aerosol (for inhalation).
- Hepatic dysfunction may dramatically increase glucocorticoids half-lives.
- During pregnancy the only safe glucocorticoid is **prednisone**, it is a prodrug that is not converted to the active compound **prednisolone** in the

fetal liver. Also any **prednisolone** formed in the mother is biotransformed to **prednisone** by the fetus.

Note: Cortisone, desoxycorticosterone, triamcinolone can be given I.M, while **dexamethasone, hydrocortisone, methylprednisolone &prednisone** can be given I.M or I.V. **Beclomethasone, flunisolide, fluticasone** & **triamcinolone** can be given as inhaler. Also **Beclomethasone, dexamethasone, hydrocortisone** & **triamcinolone** can be used topically.

- Dose selection is affected by many factors, including glucocorticoid versus

mineralocorticoid activity, duration of action, type of preparation & time of day of the drug administration. Large doses of the hormone administered for more than 2 weeks cause suppression of the hypothalamic- pituitary-adrenal (HPA) axis. The alternate-day administration is a useful regimen that can allows the HPA axis to recover/ function on the days at which the hormone is not taken.

Adverse effects:

Long- term corticosteroid therapy can cause:

1. Osteoporosis (most common) because glucocorticoids inhibit intestinal absorption of Ca^{2+}, inhibit bone formation & decrease sex hormone synthesis (patient is advised to take calcium & vitamin D supplements).
2. Increased appetite, but it is one of the reasons for the use of **prednisone** in cancer chemotherapy.
3. Cushing – like syndrome (redistribution of body fat, puffy face, hirsutism, acne, HT, insomnia & increased appetite can occurs when excess corticosteroids are present.
4. Decreased growth in children, impaired wound healing & increased risk of infection.
5. Emotional disturbances (euphoria, depression).
6. Hypertension & peripheral edema.
7. Peptic ulcer.
8. Glaucoma & cataract may occur with long- term corticosteroid therapy.
9. Hyperglycemia that may develop to D.M. (diabetic should monitor their blood glucose & adjust their medication accordingly).
10. Hypokalemia (can be counteracted by potassium supplementation).

Note: Coadministration of hepatic inducer or inhibitor drugs may require dose adjustment of glucocorticoids

Withdrawal

Withdrawal from these drugs can be a serious problem because, if the patient has experienced HPA suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal. This risk, coupled with the possibility of psychological dependence on the drug and the fact that withdrawal might cause an exacerbation of the disease, means the dose must be tapered according to the individual, possibly through trial and error. The patient must be monitored carefully.

Inhibitors of adrenocorticoid biosynthesis or function

Several substances have proven to be useful as inhibitors to the synthesis or function of adrenal steroids:

1. **Metyrapone:**

- Interferes with the final step of glucocorticoid synthesis, leading to an increase in 11-deoxycortisol & adrenal androgens & the potent mineralocorticoi 11- deoxycorticosterone.
- Used for adrenal function tests & treatment of pregnant women with Cushing's syndrome
- Can cause salt & water retention, hirsutism, dizziness & GI disturbances.

2. **Aminoglutethimide:**

- Inhibits the conversion of cholesterol to pregnenolone, reducing the synthesis of all corticosteroids.
- Used in treatment of breast cancer (it has largely replaced by tamoxifen), it is used in conjunction with dexamethasone. Also it is used in treatment of adrenal cortex malignancies.

3. **Ketoconazole:**

- Antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis.
- Used for the treatment Cushing's syndrome.

4. **Trilostane:**

- Inhibits aldosterone, cortisol & gonadal hormone synthesis.
- Causes GI side effects.

3. **Mifepristone:**

- At high doses it is a potent glucocorticoid antagonist as well as antiprogestin.

- Its use is limited for the treatment of inoperable patient with ectopic ACTH syndrome.

6. **Spironolactone:**

- Antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney.
- It can also antagonize aldosterone & testosterone synthesis.
- Effective against hyperaldosteronism.
- Useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle.
- Adverse effects are hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

7. **Eplerenone:**

- It blocks the mineralocorticoid receptor (aldosterone antagonist), thus gynecomastia that is associated with the use of **spironolactone** is not occurred with the use of **eplerenone**.
- Approved as an antihypertensive.