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AN ONGOING CE PROGRAM
of the University of Connecticut School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- RECALL the physiology of cortisol, including its regulation and effects on the body's major systems.
- DESCRIBE the pathophysiology, presentation, and evidence-based treatments of Cushing's syndrome and Addison's disease.
- ANALYZE patient case scenarios and determine whether a new intervention or adjustment of a current regimen related to cortisol levels is appropriate.
- IDENTIFY common misinformation tactics and strategies to combat them through patient education.

After completing the continuing education activity, pharmacy technicians will be able to

- RECALL the physiology of cortisol, including its regulation and effects on the body's major systems.
- DESCRIBE the pathophysiology and presentation of Cushing's syndrome and Addison's disease.
- OUTLINE evidence-based treatments of Cushing's syndrome and Addison's disease.
- RECOGNIZE common misinformation tactics and strategies to combat them through patient education.

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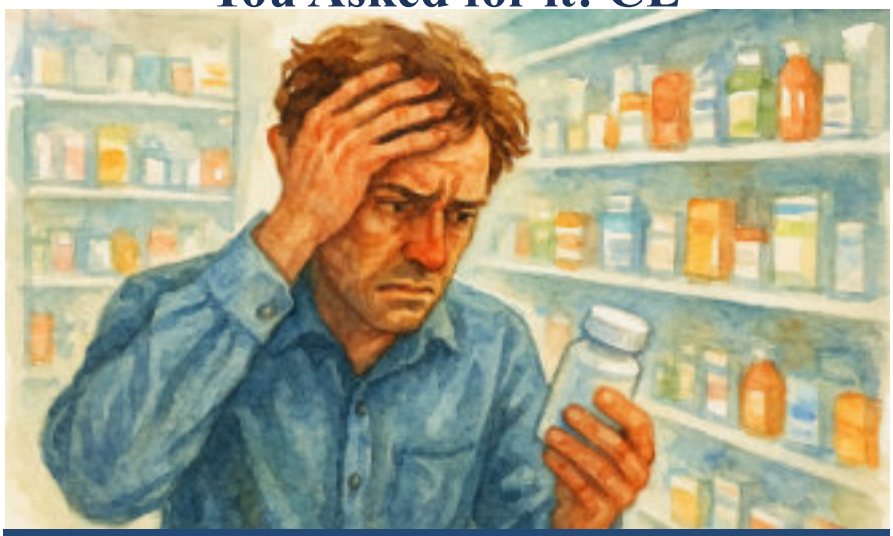

PATIENT SAFETY: ADRENAL DRAMA: HOW STRESS BECAME A MARKET

TARGET AUDIENCE: Pharmacists and pharmacy technicians who filed questions about information promulgated on social media.

ABSTRACT: Cushing's syndrome and Addison's disease are manifestations of inappropriately high or low cortisol, respectively. Both wreak havoc on patients' lives, affecting cardiac health, metabolism, and more. Social media trends have highlighted the negative effects of abnormal cortisol levels, especially high cortisol. They also talk up supplements and lifestyle practices to reduce cortisol levels. It is important for pharmacists to understand these disease states, both to treat patients who are diagnosed with them and counsel others regarding information they hear online. Treatment of Cushing's syndrome may be surgical, pharmacologic, or both. Steroidogenesis inhibitors and the glucocorticoid antagonist mifepristone are the most common medications used for Cushing's syndrome. The treatment of Addison's disease focuses on cortisol replacement with glucocorticoids. Pharmacists' expertise primes them to counsel patients on medications and recognize important signs and symptoms of cortisol-related disease states. Pharmacy technicians can play an important role in recognizing

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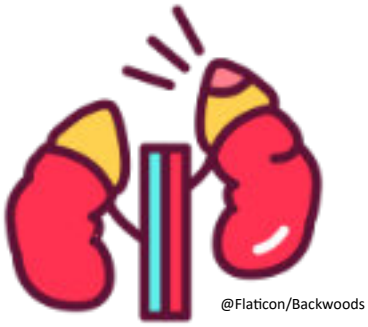
INTRODUCTION

We often refer to cortisol as the "stress hormone" for good reason. The body releases it during acute, chronic, or traumatic stress as part of a fight or flight response. To keep the body on high alert during stressful situations, it decreases insulin and increases glucagon for quick energy, suppresses inflammation, increases blood pressure, and encourages wakefulness.[1] While this whole-body reaction can be quite useful in scenarios like running from an axe murderer or

Table 1. Opposing High vs. Low Cortisol Symptoms[1,2]	
High Cortisol	**Low Cortisol**
Weight gain	Unintentional weight loss & loss of appetite
Hyperglycemia	Hypoglycemia
Hypertension	Hypotension
Hirsutism	Body hair loss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trying a new HIIT workout class, we don't need our cortisol levels running high all the time.

Having excess or insufficient cortisol can cause significant damage to the body over time. **Table 1** describes how high and low cortisol cause quite opposite effects.

Unraveling the HPA Axis

The adrenal glands produce cortisol and are a part of the hypothalamic-pituitary-adrenal (HPA) axis. Understanding the axis is key to knowing how the body makes and regulates cortisol.[3]

The HPA axis is a system made up of three parts named in its title: the hypothalamus, the pituitary gland, and the adrenal glands.

- When a person is stressed, the sympathetic nervous system (SNS) acts as a gas pedal to rev up the HPA axis.
- When the SNS signals the hypothalamus, it releases corticotropin-releasing hormone (CRH).
- CRH signals the pituitary gland to release adrenocorticotropic hormone (ACTH).
- ACTH signals the adrenal glands to release cortisol.
- Cortisol signals the whole body to respond to the stressful trigger.
- When the stressful event is over, the parasympathetic nervous system (PNS) acts as a brake, slowing the flow of hormones in the HPA axis.[3]

Stress upregulates a properly responsive HPA axis and rest downregulates it. Both improper upregulation and downregulation can cause health issues, named as Cushing's syndrome (CS) and Addison's disease (AD), respectively.

THE "CORTISOL CRAZE"

Despite the relative rarity of diagnosed cortisol abnormalities, related hashtags on social media have racked up millions of views.[4]

NOTE: About 6 people in a million are diagnosed with Addison's disease and 49 people in a million are diagnosed with CS in the United States each year.[5]

The major concern for most people sharing online is chronic stress, leading to high cortisol. Low cortisol can be just as debilitating, but the Cushingoid appearance seems to be the highlight in advertising. A Cushingoid appearance is a catch-all term for the physical signs and symptoms of high cortisol, including excess weight in the face, abdomen, back of the neck, and chest, excess body hair, limb atrophy, acne, and easy bruising.[6-8] Users selling supplements and diet plans often refer to the product reducing "cortisol face" and "cortisol belly."[9-11] "Cortisol detoxing" is another trend focused on weight loss and improved mood by reducing stress, thus reducing cortisol.[12]

The question is whether symptoms are severe enough to require intervention. It seems that urgent concern about cortisol itself is unproductive, but focusing on lowering daily stress may be beneficial for those in this scenario. A wide gap exists between being stressed and being diagnosed with CS (discussed in more detail below).

Safety and Efficacy of Select Supplements and Natural Remedies

So, if a patient comes to the pharmacy counter saying she wants to lower her cortisol, are any common supplements safe and effective? Let's dig further into a couple of supplements touted for their ability to lower cortisol.

Supplement companies advertise ashwagandha for improving sleep and reducing stress and anxiety. Influencers sometimes include it on posts listing supplements to lower cortisol. Per NatMed Pro, tolerability in adults is established for a maximum dose 1250 mg daily when used for up to six months, and adverse effects are generally mild, including gastrointestinal (GI) upset, nausea, and drowsiness. Notably, ashwagandha should not be taken during pregnancy due to potential abortifacient effects.[13,14] Small studies suggest that it may be effective for stress, anxiety, and poor sleep quality.[13,14] One meta-analysis and a small randomized control trial (RCT) found a statistically significant reduction in perceived stress, Hamilton Anxiety score, and serum cortisol levels.[15,16] However, the authors of the meta-analysis admit that it is difficult to apply these results clinically due to major differences between included studies, and the RCT only included 60 patients.[15,16] Weak evidence suggests that ashwagandha may lower cortisol by reducing stress response.

L-theanine is another supplement advertised as a cortisol-lowering agent. L-theanine is an amino acid found in tea leaves. Advertisements mainly highlight increased relaxation, lower stress and anxiety, and improved sleep. It is considered fairly safe, but evidence of efficacy is weak. Adult patients have tolerated doses of up to 900 mg daily used for up to eight weeks.[17] It is unlikely to cause harm but the potential benefits remain murky.[18]

Lifestyle interventions promoted on social media often focus on reducing chronic stress. Things like good sleep, frequent exercise, and healthy eating can benefit everyone.[19] Chronic stress can heighten cortisol levels, but this type of cortisol elevation is significantly different than having CS. Most lifestyle changes will benefit patients to some extent. Note that although stress-reducing lifestyle changes have benefits, a patient with CS will need further medical intervention for the best outcomes.

If a patient truly has symptoms of high cortisol, it is worthwhile to see a healthcare provider for a full workup. Over-the-counter supplements are not a substitute for prescription medications and monitoring by a licensed provider.

HIGH CORTISOL DUE TO CUSHING'S SYNDROME

Patient case: Eva is 38-year-old female patient with a past medical history of hypertension and prediabetes. She presents to the clinic reporting recent health changes. In particular, Eva says that her blood sugar and blood pressure, which she self-monitors at home, have been higher than usual lately. She also describes bruising with no known source or after events that would not have elicited a bruise in the past. When asked if there's been any recent changes to her lifestyle or medications, Eva notes that she's been gaining weight despite maintaining frequent exercise and a healthy diet. She feels that the weight gain is most visible in her face and abdomen.

PAUSE AND PONDER: Which of Eva's symptoms are red flags? What stands out to you?

Pathophysiology of Cushing's Syndrome

Patients with CS, or chronic high cortisol, either have an exogenous or endogenous cause of disease. The most common cause is several months of continuous exogenous exposure to glucocorticoids. Patients taking steroids for asthma, autoimmune disease, and other conditions may be at risk. Endogenous CS affects 2-3 people per million.[6] About 80% of those rare cases result from an ACTH-dependent tumor, while the other 20% are associated with an ACTH-independent cause.[6]

The most common CS patient is a female in her 20s or 30s, although men and people of other ages can have CS.[6] Seventy percent of patients with CS are women, and most are under the age of 50.[7]

Table 2. Signs and Symptoms of CS[6-8]

Rapid weight accumulation in the face (moon face), abdomen, back of the neck (buffalo hump), and chest	Red, round face
Poor wound healing	Hypertension
Hirsutism	Diabetes
Purple striae	Easy bruising
Fatigue	Blurry vision and dizziness
Muscle weakness and atrophy of limbs	Libido changes and/or erectile dysfunction
Irritability	Acne

Presentation and Complications

Table 2 lists common signs and symptoms that may be present in patients with CS. Encourage patients experiencing several of these symptoms to speak with a provider, especially if they are on a corticosteroid.

NOTE: Hirsutism is excessive dark hair growth, especially on the face and body. Patients may also experience balding on their head. Striae are stretch marks, which are large, purple, and often seen on the abdomen in CS patients.[7]

CS can significantly reduce patients' quality of life. Physical changes, like weight gain and excess body hair, may be embarrassing to some.[7] Some recent studies associate psychiatric symptoms, especially depression, with the onset of CS. Most patients who experience depression with CS improve with correction of high cortisol, but depression may not completely resolve.[20] Untreated CS has consequences beyond the list of signs and symptoms. **Table 3** lists high-risk complications that patients with active CS are at risk of developing. While they are at highest risk with active CS, some risk factors may persist after remission and require further treatment.[21]

Table 3. Complications of Active CS[6,21]

Cardiovascular Complications	Metabolic Complications	Other
Arterial hypertension	Insulin resistance	Higher infection risk
Atherosclerosis	Glucose impairment	Myopathy
Heart failure	Visceral obesity	Neuropsychiatric disorders
Hyperlipidemia		Osteoporosis
Thrombosis		

Table 4. Cortisol Testing[8,22]	
Testing Method	**Description**
24-hour urinary free cortisol	Multiple urine collections over 24 hours tested
Midnight plasma/ late-night salivary	Blood or saliva level taken at night for ≥2 nights Saliva samples can be done at home
Overnight dexamethasone suppression test	The patient receives 1 mg of dexamethasone late at night Cortisol measured the next morning
Low-dose dexamethasone suppression test	The patient receives low-dose dexamethasone by mouth every six hours for two days Multiple urine collections starting before the first dose and continuing through the test

NOTE: Due to the increased risk of infection, CS patients benefit from age-appropriate vaccines like influenza, *Herpes zoster*, and pneumonia.[20]

Testing Cortisol Levels for Cushing's Syndrome

Clinicians have several ways to determine if a patient's cortisol levels are above normal limits. Common test strategies include a 24-hour urinary free cortisol test, midnight plasma cortisol/late-night salivary cortisol, and dexamethasone suppression tests.[22] Note that two of the options include specific times of day for measurement. Cortisol is usually lower at night, so abnormally high measurements at night are notable. **Table 4** highlights the differences between testing options.

Treatment

Treatment of CS depends on the cause. For those with an exogenous source of cortisol causing the issue, tapering down or completely off the causative glucocorticoid will return cortisol to normal limits.[7] For those with an ACTH-dependent tumor causing CS, the 2015 Endocrine Society Clinical Practice Guidelines recommend surgical removal of the tumor if possible.[23] After surgery, a patient may have hypocortisolism, hypercortisolism, or eucortisolism. Eucortisolism does not need further treatment.[23]

If patients experience hypocortisolism after surgery, they will require glucocorticoid replacement. Patients must be monitored every six hours for 24-72 hours after pituitary surgery for ACTH abnormalities. Use of glucocorticoids intraoperatively and postoperatively varies by institution. Providers may start glucocorticoids during surgery or wait to see if the patient starts displaying signs of adrenal insufficiency before starting glucocorticoids. All patients with a cortisol level less than 5 mcg/dL and some with a level 10 to 15 mcg/dL will require replacement. The recommend dosing of hydrocortisone to a physiologic level is 10 to 12 mg/m^2/day in divided doses. Some institutions may use supraphysiologic replacement up to 20 mg of hydrocortisone two to three times daily with a 2- to 4-week taper.[24]

Several options are available for those who don't qualify for surgery or who continue to experience hypercortisolism after surgery. These include repeat surgery, radiation therapy, or pharmacological treatment. This CE will mainly focus on the pharmacologic options.

Three types of medications can treat CS[25]:

- **Steroidogenesis inhibitors**, which block the enzymes that make cortisol.
- **Glucocorticoid antagonists**, which block cortisol's action by preventing it from binding to its receptor.
- **ACTH neuromodulators**, which inhibit pituitary action, block the signal to the adrenals to release cortisol.

Table 5 provides a complete list of medications in each class.

Steroidogenesis inhibitors are the most commonly used medications for CS. They can be used on their own or as an adjunct treatment. See pros and cons to consider for each medication in **Table 6** on pages 5 and 6.[23,25]

The glucocorticoid antagonist mifepristone is used as primary therapy or after a failed surgery in patients with diabetes and/or uncontrolled high blood sugar in CS.[23,26] However, mifepristone can also be used in medical abortions. Prescribing and dispensing mifepristone can be complicated in the United States as a result of the indication for terminating pregnancy. More than 10 states restrict mifepristone's use. Some ban its use entirely, while others only allow mifepristone prescriptions from certified providers and dispensing from authorized pharmacies.[26,27] Despite the controversy, mifepristone remains a highly effective treatment option for CS.[25-27] See **Table 6** on the next page for more information.

Table 5. Medications Used to Treat CS[25]		
Steroidogenesis inhibitors	**Glucocorticoid antagonist**	**ACTH Neuromodulators**
Etomidate Ketoconazole Levoketoconazole Mitotane Metyrapone Osilodrostat	Mifepristone	Cabergoline Pasireotide

Table 6. Clinical Pearls for Common CS Medications[25,27-32]		
Medication	**Dosing**	**Clinical Pearls**
Steroidogenesis Inhibitors		
Etomidate	0.03 mg/kg IV bolus 0.1–0.3 mg/kg/h	Off-label for CS Administered parenterally Rapid maximum effect, around 11 hours Requires intensive inpatient monitoring (not for long-term use)
Ketoconazole	TDD of 200 to 1,200 mg, split 2-3 times daily	Off-label for CS Rapid onset but can take weeks for full effect Decreases testosterone Boxed warning: liver toxicity Adverse effects include GI symptoms, gynecomastia, skin rash, edema, transient LFT elevations and rarely hepatotoxicity Monitor EKG (QT prolongation) and LFTs Requires low gastric pH for absorption Major CYP3A4 substrate and strong inhibitor, potential for significant drug interactions
Levoketoconazole	TDD of 300 mg to 1.2 g, split BID	Monitor EKG (QT prolongation) and LFTs Most common adverse events include GI symptoms, headache, arthralgias, myalgias, and fatigue Major CYP3A4 substrate and strong inhibitor, potential for significant drug interactions
Mitotane	TDD of 500 mg to 8 g, split TID	Off-label for CS Teratogenic Maximum effect after 2-3 months of treatment Adverse effects include GI symptoms, impaired mentation and dizziness, gynecomastia, rash, elevated LFTs, and hypercholesterolemia Almost 30% of patients discontinue treatment due to adverse effects Give largest dose in the evening
Metyrapone	TDD 500 mg to 6 g, split up to 4 times daily	Off-label for CS Cortisol levels decrease within two hours of administration May be used with caution in pregnancy Take with food Adverse effects include GI symptoms, hirsutism, hypertension, and hypokalemia
Osilodrostat	TDD 2 to 14 mg, split BID Max maintenance TDD is 60-80 mg	Monitor EKG Initial dose adjustments for moderate-severe renal impairment Effective in hours-days Note drug interactions Adverse effects include GI symptoms, arthralgia, dizziness, hypertension
Glucocorticoid Antagonist		
Mifepristone	300 to 1,200 mg once daily	FDA approved to control hyperglycemia due to hypercortisolism Also used to terminate pregnancy- providers must confirm negative pregnancy status in patients of childbearing potential prior to starting this medication Has a REMS program Monitor thyroid function Major CYP3A4 interactions Adverse effects include nausea, fatigue, headache, hypokalemia, hypertension, abnormal vaginal bleeding

Table 6. continues at the top of page 6

Table 6. Clinical Pearls for Common CS Medications[25,27-32] CONTINUED

ACTH Neuromodulators		
Cabergoline	0.5 to 4 mg total per week, split twice weekly	Off-label for CS Requires cardiac valve monitoring Adverse events include GI symptoms and dizziness May cause psychiatric effects; not recommended with history of bipolar or impulse disorder
Pasireotide	0.3 to 0.9 mg twice daily OR 10-40 mg per month	BID formulation given via subcutaneous injection, monthly formulation is via intramuscular injection Maximum dose of 0.6 mg BID or 20 mg monthly in moderate hepatic impairment Monitor glucose, LFTs, EKG Not recommended in diabetes

ABBREVIATIONS: BID (two times daily), CYP3A4 (cytochrome P450 3A4), EKG (electrocardiogram), GI (gastrointestinal), LFTs (liver function tests), TDD (total daily dose), TID (three times daily)

Providers may use ACTH neuromodulators as monotherapy or an adjunct option. Cabergoline is an off-label medication for CS, but both formulations of pasireotide are FDA-approved. Pasireotide offers convenient dosing as an intramuscular injection every four weeks but comes with a high risk of hyperglycemia. Three quarters of patients managed with pasireotide require other medication for glucose management.[28]

Only patients with an established diagnosis of CS and active signs and symptoms require treatment. Patients without an established diagnosis or borderline abnormalities with no signs and symptoms are unlikely to benefit from treatment.[23]

SIDE NOTE: Metyrapone and mifepristone appear on the ISMP List of Look-Alike drug names. Be careful not to confuse metyraPONE with metyroSINE and miFEPRIStone with miSOPROStol.[33]

Recently Approved Agents

The adverse effects from current CS medications are less than ideal. As a result, researchers are looking for new ways to treat the disease.

The Food and Drug Administration (FDA) approved osilodrostat (Istrusia), an oral medication for CS, in March 2020. Patients start on 2 mg twice daily and titrate by 1 to 2 mg every two weeks based on tolerability and clinical response. Most patients can be maintained on 2 to 7 mg twice daily and the maximum dosage is 30 mg twice daily.[34] It works by preventing cortisol synthesis by inhibiting the 11-beta-hydroxylase enzyme.[35] Clinical trials included patients who were not cured by surgery or who were not surgical candidates. In a phase 3 trial, significantly more patients in the osilodrostat group had cortisol levels within normal limits (n = 37, 77.1%) than in the placebo group (n=2, 8%) by week 12. By week 36, over 80% (n = 40) of patients in the osilodrostat group achieved normal cortisol. As a result, the drug improved signs of CS, like weight, fasting plasma glucose, blood pressure, and cholesterol.[36] Common adverse effects included adrenal insufficiency, headache, nausea and vomiting, fatigue, and edema. Rare but serious adverse effects include QTc prolongation and androgen elevation.[35]

Levoketoconazole (Recorlev) is another recently approved medication for CS as of December 2021. Patients start on 150 mg twice daily and titrate up by 150 mg/day every two to three weeks based on tolerability and cortisol levels. The maximum dose is 600 mg twice daily.[37] It is a stereoisomer of ketoconazole, which is thought to be more potent than a racemic mix. A single-armed study of 94 patients found that 31% (n = 29) of patients in the intention-to-treat population responded to treatment with levoketoconazole. Despite the increased potency allowing for a lower dose compared to ketoconazole, almost all patients (n=92, 98%) experienced an adverse event. The most common were nausea, headache, and peripheral edema. Rare but serious events included prolonged QT interval, abnormal liver function tests, and adrenal insufficiency.[38]

It is important to note that CS is considered an orphan disease due to its rarity.[35] Randomized controlled trials are often small, with fewer than 100 patients in the population of some phase 3 trials. These new medications are not incorporated into the most recent guidelines. This is reflective of the age of the most recent Endocrine Society guidelines, which came out in 2015, not the effectiveness or appropriateness of newer medications. Use of newer medications is likely to be reflected when new guidelines come out.

LOW CORTISOL DUE TO ADDISON'S DISEASE

Patient case: Liam is a 56-year-old man who arrives at the emergency department (ED) after three days of severe nausea and vomiting. He says his wife made him come in because she's worried that he's dehydrated. He reveals that he has new joint pain with this illness and it's getting worse, up to a 7/10 on the pain scale. Liam reports that he spent most of the morning sitting

on the floor of his bathroom because he feels lightheaded when he stands up and is afraid that he'll fall. The ED physician completes a physical exam and notes that Liam's skin is darker in some areas, like his gums, palm creases, and knuckles.

PAUSE AND PONDER: What testing is necessary to determine the cause of Liam's condition? Do his symptoms sound like a run-of-the-mill virus? Something else?

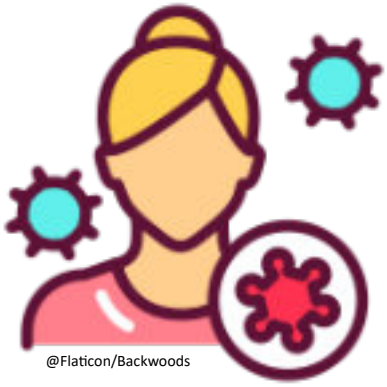
Pathophysiology of Addison's Disease

Addison's disease (AD), named after Thomas Addison, who discovered the disease, is adrenal insufficiency. The patient's body does not produce enough cortisol. There are three different etiologies[39]:

- Primary: destruction of the adrenal cortex
- Secondary: insufficient production of ACTH
- Tertiary: insufficient stimulation of the adrenal gland by CRH

Primary AD can be either congenital or acquired. Most cases of congenital AD are linked to a genetic mutation affecting cortisol and aldosterone synthesis. On the other hand, autoimmune adrenalitis is the main cause of acquired AD. Although they remain uncommon causes in the United States, tuberculosis and human immunodeficiency virus infections can also trigger AD.[39]

NOTE: Autoimmune adrenalitis is when the immune system attacks and destroys the adrenal glands with no known reason. It takes months to years of active autoimmune adrenalitis for symptoms of AD to show.[40]



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Secondary AD is due to a deficiency in ACTH secretion or a pituitary adenoma. Pituitary adenomas tend to cause deficiencies in all pituitary hormones.[39]

Tertiary AD has an exogenous cause, usually sudden withdrawal from long-term corticosteroid use. This is why tapering corticosteroids matters; slowly reducing exogenous corticosteroids allows the body to adjust and helps prevent withdrawal. Providers should also warn patients not to self-discontinue corticosteroids. Sometimes chronic opioid use can cause tertiary AD by suppression of the entire HPA axis.[39]

Presentation and Complications

Table 7 lists common signs and symptoms of AD. It is important to note that primary AD tends to present with more severe symptoms than secondary AD and have aldosterone abnormalities. Patients with secondary AD still have some cortisol and aldosterone may remain normal. These patients are unlikely to experience hyperpigmentation, dehydration, or hyperkalemia. Tertiary AD differs in that patients may experience a mix of Cushingoid appearance and AD symptoms.[39]

Patients with AD may experience acute, life-threatening symptoms during severe injury, illness, or stress. This is known as an Addisonian crisis or acute adrenal failure. Hallmarks of the crisis include extreme pain and weakness, mental status changes, severe vomiting and diarrhea, hypotension, and possibly loss of consciousness.[2]

Testing Cortisol Levels for Addison's Disease

Patients with signs and symptoms of AD should undergo a corticotropin stimulation test. In the test, patients receive 250 mcg of IV corticotropin. If the patient's cortisol does not reach at least 500 nmol/L at 30 or 60 minutes, it indicates AD. Plasma ACTH is helpful to determine if a patient's AD is primary in nature. High ACTH indicates primary AD.[41]

PAUSE AND PONDER: What medications are available to replace cortisol?

Table 7. Signs and Symptoms of AD[2,39]

Fatigue	Hyperpigmentation (scars, skin creases, gums)
Abdominal pain	Nausea and vomiting
Diarrhea	Loss of appetite, unintentional weight loss
Muscle and joint pain, muscle spasms	Dehydration
Hypotension	Irritability, depression, poor concentration
Craving salty food	Hypoglycemia
Hair loss	Abnormal menstruation
Hyperkalemia	Hyponatremia

Treatment of Addison's Disease

AD requires steroid replacement. Treatment for primary AD is lifelong. Patients with secondary and tertiary AD may require long-term treatment with a gradual taper or treatment for life. Appropriate choices for glucocorticoid replacement include 15 to 25 mg of oral hydrocortisone or 20 to 35 mg of cortisone acetate per day. If the hydrocortisone formulation is not modified-release, patients will need to take it two to three times per day. The first dose of the day should be the largest and no more than a maximum of 10 mg. Taking a steroid close to bedtime can disturb sleep and should be avoided.[39,41]

When possible, providers should avoid prescribing avoid prednisolone and dexamethasone. Prednisolone has a higher risk of dyslipidemia and bone weakening compared to other glucocorticoids. The advantage is the lower dosing frequency of one to two times daily, which may increase adherence. Dexamethasone has an extremely long half-life, increasing the risk of Cushingoid adverse effects significantly.[39,41]

Monitoring and adjusting glucocorticoid treatment should be based on patients' signs and symptoms, not hormonal monitoring. In particular, providers must track body weight, postural blood pressure, energy levels, and Cushingoid symptoms at baseline and throughout treatment.[41]

Adjusting the dose of glucocorticoids is necessary in stressful situations, like surgery, severe illness, and pregnancy. More severe conditions, like major surgery and childbirth, require higher dosing than average illnesses. Patients may develop adrenal crisis if they take the same glucocorticoid dose during more stressful times.[41]

Side note: Mineralocorticoid replacement in aldosterone deficiency is not the focus of this CE, but it is still important to mention. Patients with primary AD require mineralocorticoid replacement, while secondary and tertiary AD do not. Destruction of the adrenal gland in primary AD creates a deficiency in all hormones it produces. Secondary and tertiary AD are related to ACTH signaling, which does not affect aldosterone production. The treatment is 0.05 to 0.2 mg of fludrocortisone each morning. Monitoring blood pressure and electrolytes is necessary.[39]

Side note: Women with primary AD may also experience adrenal androgen deficiency. This manifests as low libido, depression, and low energy.[41] Dehydroepiandrosterone (DHEA) treatment may be necessary if patients still have symptoms after appropriate glucocorticoid and mineralocorticoid management. The goal is to have a normal morning serum DHEAS (sulfate-bound, stored DHEA) level.[39,41]

Emerging Treatments

New treatments for AD have focused more on modifying hydrocortisone release to improve patient satisfaction than on coming up with a brand new drug. The hydrocortisone modified-release hard capsule (Efmody) is a newer innovation to hydrocortisone that was approved by the European Commission in 2021. It is not yet available in the United States.[42]

Clinical trials are underway for a hydrocortisone subcutaneous pump, meant to closely mirror cortisol secretion. A small trial of 21 patients tested the pump. Over 6 weeks, the pump improved patients' quality of life subjectively. Patients reported waking up more easily, better mood upon awakening, and an overall positive mood.[43] Larger studies are necessary to prove the objective benefits of a pulse pump, though improvement in mood may be significant considering AD's link to irritability and depression.

One of the newest innovations under development in AD treatment is implantable cell therapy. Bioprinted tissue has the potential to replace the adrenal gland's function in primary AD patients. At this time, research is in the preclinical stage. Researchers removed the adrenal glands of mice and replaced them with bioprinted tissue in one group. When researchers injected ACTH into the mice, those with bioprinted tissue replacement responded by producing cortisol, while those with no renal replacement showed no change.[44,45] In time, bioprinted tissue may offer a permanent treatment for primary AD.

Side note: Bioprinted tissue is human tissue created in a lab. The new technology involves 3D printing bioink, a mixture of live cells and material to support cell growth, to create tissues and organs.[46]

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HANDLING MISINFORMATION AND DISINFORMATION

PAUSE AND PONDER: How would you speak to a patient that asks you about an article she saw online sharing incorrect information? What if she doesn't believe you?

Misinformation is information that is false, but not shared to cause harm. Disinformation is information that is false and deliberately shared to cause harm.[47]

People who spread misinformation and disinformation may use many strategies to distract from false claims. Tactics include[48]

- Emotional triggering, especially sparking fear or anger
- Treating anecdotes like facts
- Sharing old or outdated information

People have access to a plethora of information with the Internet. With such an overwhelming amount of information available to consume online, it can be difficult to find factual medical advice. Additionally, social media companies are lax about false posts. For example, social media sites do not take action against 95% of posts reported for COVID-19 and vaccine misinformation.[47] As healthcare providers, pharmacists can offer patients an analysis of information they find and strategies for them to evaluate information on their own in the future.

One popular way to break down how to address disinformation and misinformation with patients is the "Three C" approach. This involves

- Compassion
- Connection
- Collaboration

It is important to recognize that being a trusted source of information requires mutual respect. Communicating in a nonjudgmental and compassionate way is important. If patients think pharmacy staff are judging them for believing something incorrect, they are more likely to get defensive and close off future opportunities for discussion. Pharmacy staff should make sure patients know their intent is to help them make the best health decisions and that the conversation is worthwhile. Staff should ask patients to share more of their point of view with open-ended questions and listen.[47,49] When patients explain their point of view, it will help to pick out what matters to the patient. Cultural, individual, and social values can play a part.[47]

Connection directly links to compassion. Pharmacy staff should speak affirmatively to patients for seeking further information on a subject and acknowledge the parts of the patient's narrative that are true. When it is necessary to correct false information, pharmacists and technicians should focus more on the evidence behind the correction than on the fact that the patient was wrong. Staff should continue to ask patients if they have further thoughts and questions. Pharmacists and technicians can also ask patients where they get their medical information and suggest reputable resources for them to use in the future.[47]

At the end of the discussion, collaborate with the patient on the next steps. Trying to coerce or compel the patient to agree with everything you say often backfires. Remind patients that you're on their side when you make recommendations. Allow them to share their thoughts and ask further questions about those recommendations.[47] To improve patient health literacy and confidence, consider sharing strategies to combat misinformation in the future. Online guides written in layman's terms, like the ones posted by San Diego Circuit (https://libguides.sdsu.edu/health/avoid-misinformation) libraries and the Department of Health and Human Services (https://www.hhs.gov/surgeongeneral/reports-and-publications/health-misinformation/index.html), can help patients analyze other misinformation they come across.[50,51]

Given the heavy discussion of cortisol on social media, pharmacists and technicians may run into situations where patients talk to about false or overstated claims. Keep compassion, connection, and collaboration in mind when this happens.

CONCLUSION

The adrenal glands produce cortisol, which is necessary to respond to stress. However, when the adrenals release too much or too little cortisol, it can cause serious problems. Despite the rarity of adrenal diseases, people have been discussing cortisol, especially high cortisol, on online platforms. It has become a way to advertise supplements to reverse perceived symptoms of high stress. CS is treated first with surgery or cessation of exogenous steroids when possible. Medication therapy is still important and necessary for many CS patients. AD patients require long-term glucocorticoids, which may sometimes be for life. Pharmacists play an important role in educating patients on CS and AD medications. They can also break down expectations versus the low-evidence reality with "cortisol-lowering" supplements, while still validating patient concerns.

Figure 1 summarizes key points that pharmacy teams can use with interested patients.

Figure 1. Checking Cortisol Claims Closely

Best

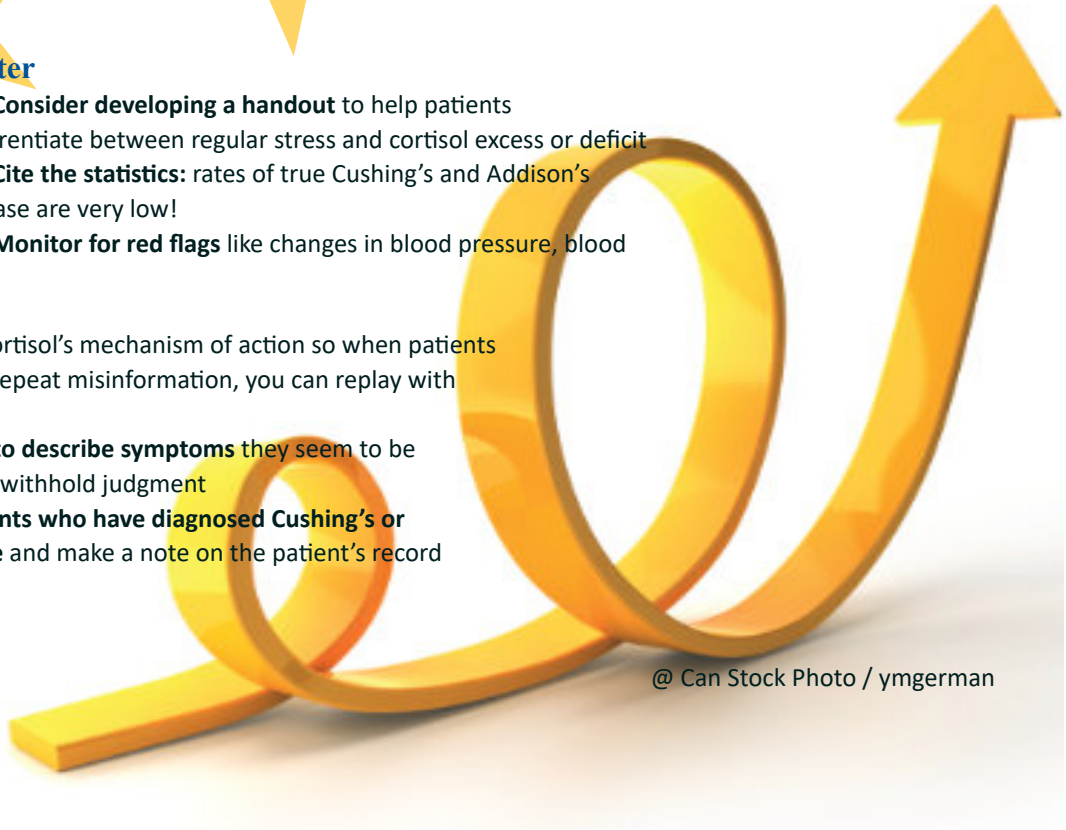
1. **Be COMMUNITY CHAMPIONS** and gently correct social media posts when they make exaggerated claims
2. **Encourage discussion** with patients about stress and best ways to handle it
3. **Collaborate actively with prescribers** when patients present with symptoms that need attention

Better

1. **Consider developing a handout** to help patients differentiate between regular stress and cortisol excess or deficit
2. **Cite the statistics:** rates of true Cushing's and Addison's disease are very low!
3. **Monitor for red flags** like changes in blood pressure, blood

Good

1. **Remember** cortisol's mechanism of action so when patients ask questions or repeat misinformation, you can replay with confidence
2. **Ask patients to describe symptoms** they seem to be experiencing and withhold judgment
3. **Identify patients who have diagnosed Cushing's or Addison's disease** and make a note on the patient's record



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