



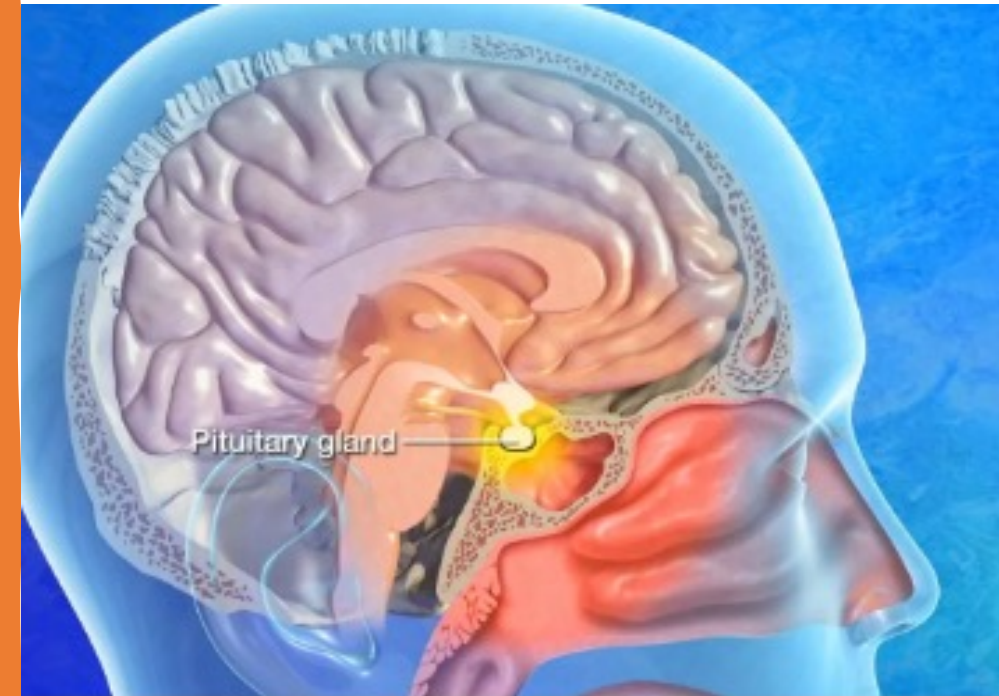
CME

Cushing's Disease Research Highlights: ENDO 2023

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Cushing's Disease Updates from

ENDO2023

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Disclosures

Research Support

- Recordati

Consulting

- Corcept

Other planners for this activity have nothing to disclose

What is Cushing's Syndrome?

A rare endocrine disorder characterized by excessive cortisol

When a pituitary adenoma secreting excessive ACTH causes this syndrome, it is called **Cushing's Disease**

Common signs and symptoms:

- Weight gain
- Hypertension
- Diabetes Mellitus
- Hirsutism, acne, hair loss, bruising
- Muscle weakness and atrophy of extremities
- Poor wound healing, infections
- Insomnia, mood changes
- Amenorrhea or irregular menstrual cycles

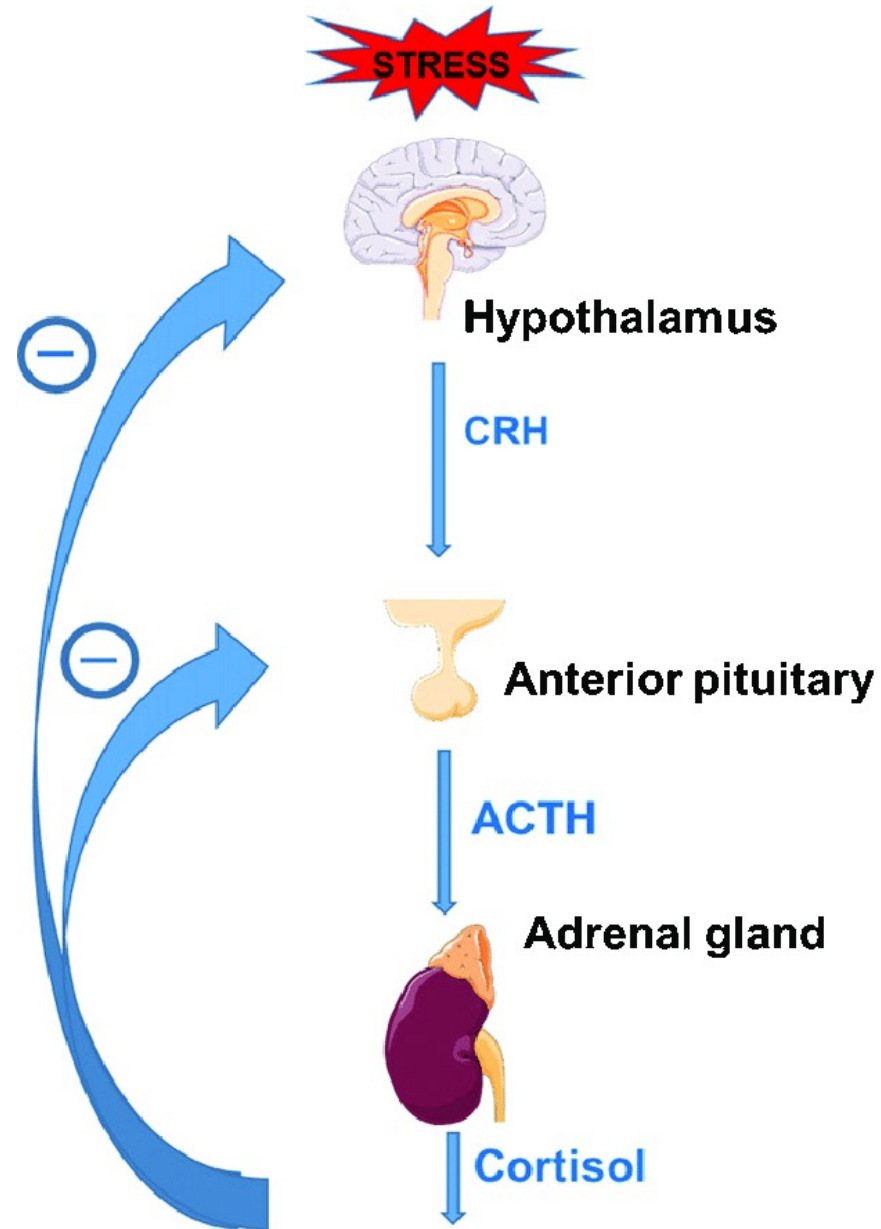
Clinical Features of Cushing's Syndrome

- facial rounding,
- supraclavicular fullness,
- posterior cervical fat pad



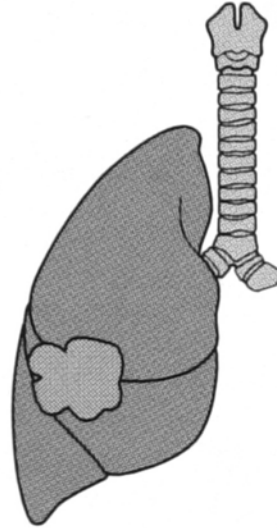
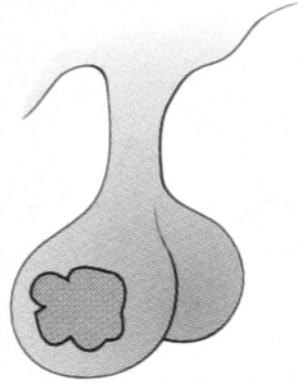
- central obesity with thin arms and legs
- striae

The Hypothalamic-pituitary-adrenal Axis



Cushing's Syndrome - 3 possible sources

Cushing's *disease*

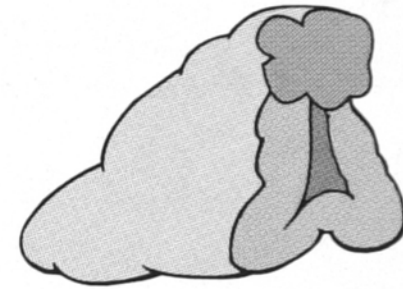


ACTH-Dependent

High or normal ACTH

Pituitary
65%–75%

Ectopic
10%–15%



Exclude exogenous source

ACTH-Independent

Low ACTH

Adrenal
15%–20%

Treatment Algorithm

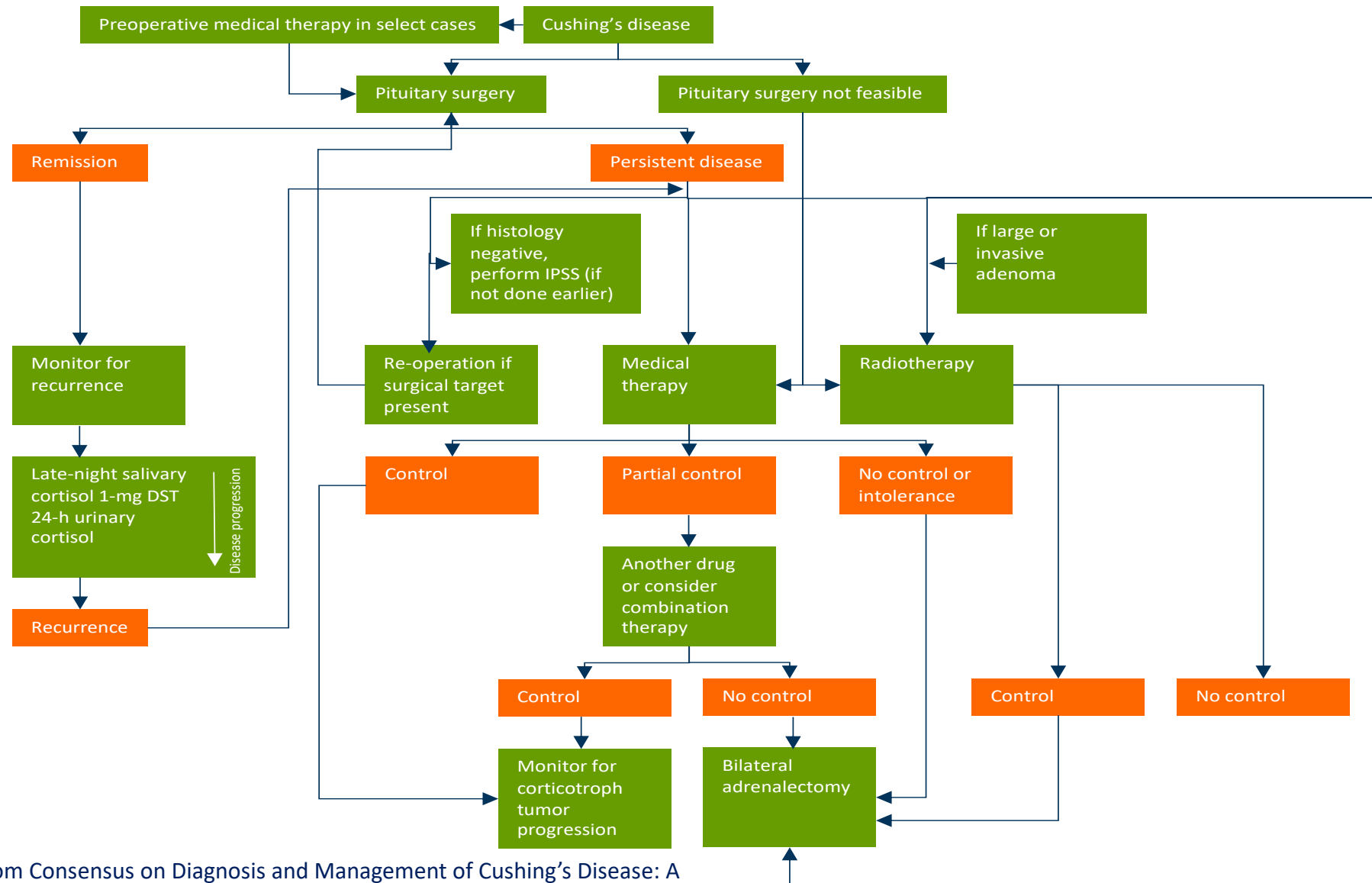
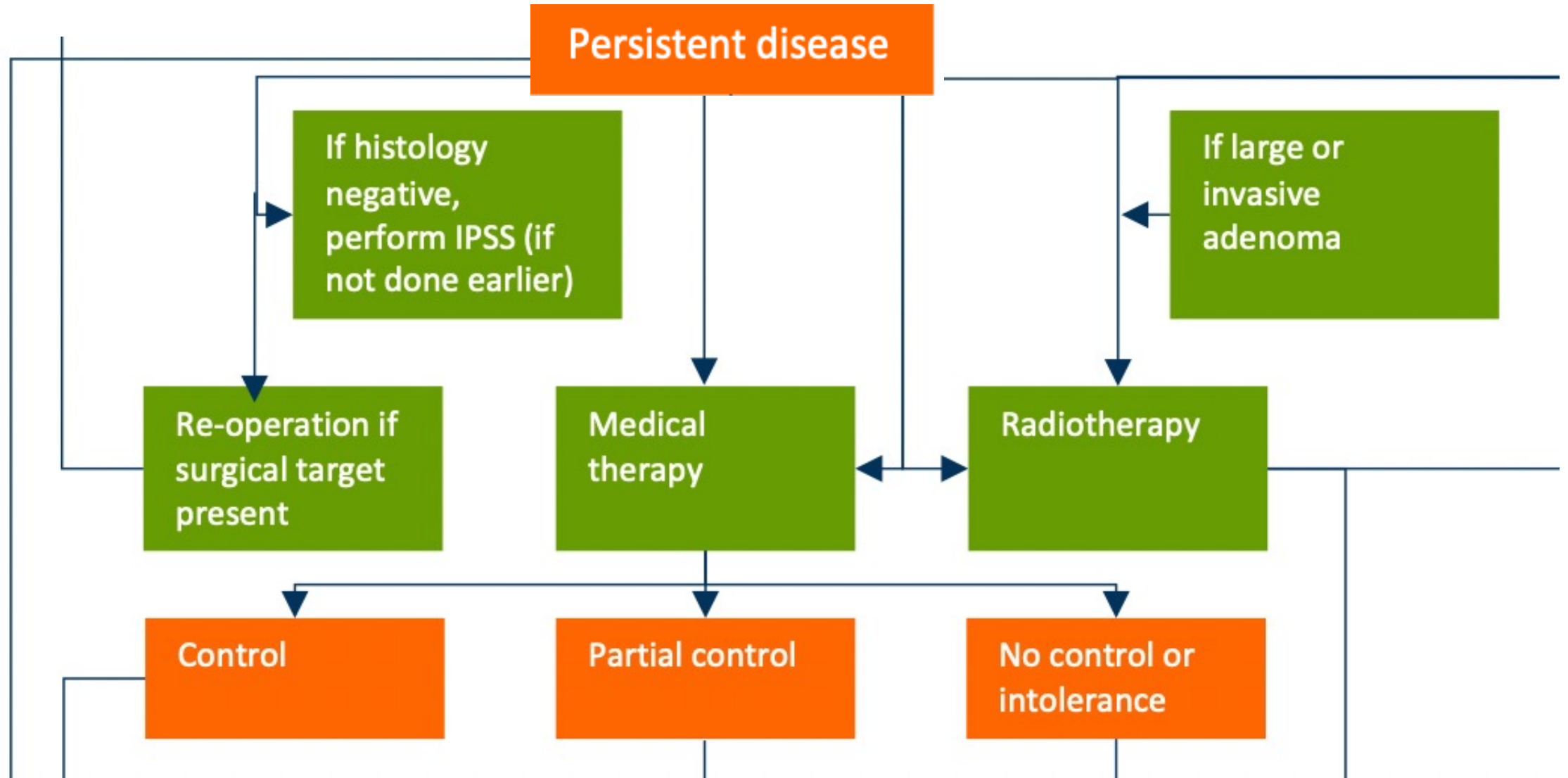


Figure recreated from Consensus on Diagnosis and Management of Cushing's Disease: A Guideline Update Fleseriu et al. *Lancet Diabetes Endocrinol.* 2021;9:847-875.

Role of Medical Therapy



Current Medicinal Therapies

Directly effects tumor

-binds to receptors on adenoma

Pasireotide- 2nd generation somatostatin receptor ligand

Cabergoline- dopamine agonist

Glucocorticoid receptor blockers

Mifepristone

Adrenal steroidogenesis inhibitors

Ketoconazole

Mitotane

Etomidate

Osilodrostat

Levoketoconazole

Metyrapone



ENDO
2023

Endocrine Society Annual Meeting

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Chicago, Illinois

Abstracts published online
and in the Journal of the
Endocrine Society

Clinical Trials



Osilodrostat Clinical Trials: LINC II, III, IV

Oral inhibitor of 11 β -hydroxylase (responsible for catalyzing final step of cortisol synthesis); also inhibits aldosterone synthesis.

- **LINC II**: A phase II study followed by an extension period.
- **LINC III**: A 48-week, phase III study with a double-blind randomised withdrawal period (four periods).
- **LINC IV**: A 12-week, randomized, double-blind, placebo-controlled period followed by a 36-week, open-label extension.
- Pooled data removed placebo data due to study design differences.

Osilodrostat pooled data (N=220) from LINC II, III, IV

Osilodrostat 2 mg twice daily (bid), with dose increases every 2 -4 weeks if mean urinary free cortisol (mUFC) > upper limit of normal (ULN).

Maximum dose was 30 mg bid in all studies (reduced from 50 mg bid in LINC 2 core phase).

	Median	95% confidence interval (CI)
Duration of therapy	100.1 weeks	1-351
Daily dose	6.8 mg	1-47
Dose needed for mUFC control.	Varied greatly	
Time to mUFC control	35 days	34-41
Time to first adverse event of special interest	12 weeks	10-15

correlated with baseline mUFC severity

Adverse events (AEs) were less frequent during long-term maintenance than dose titration.

11 discontinued due to AEs: hypocortisolism (n=8); accumulation of adrenal hormone pre-cursors (n=3)

Site of action of osilodrostat in steroid synthesis

The inhibition in the 11-beta-hydroxylase step in steroid synthesis results in **decreased cortisol and aldosterone** and **increased 11-deoxycortisol, testosterone and 11-dexoxy corticosterone**

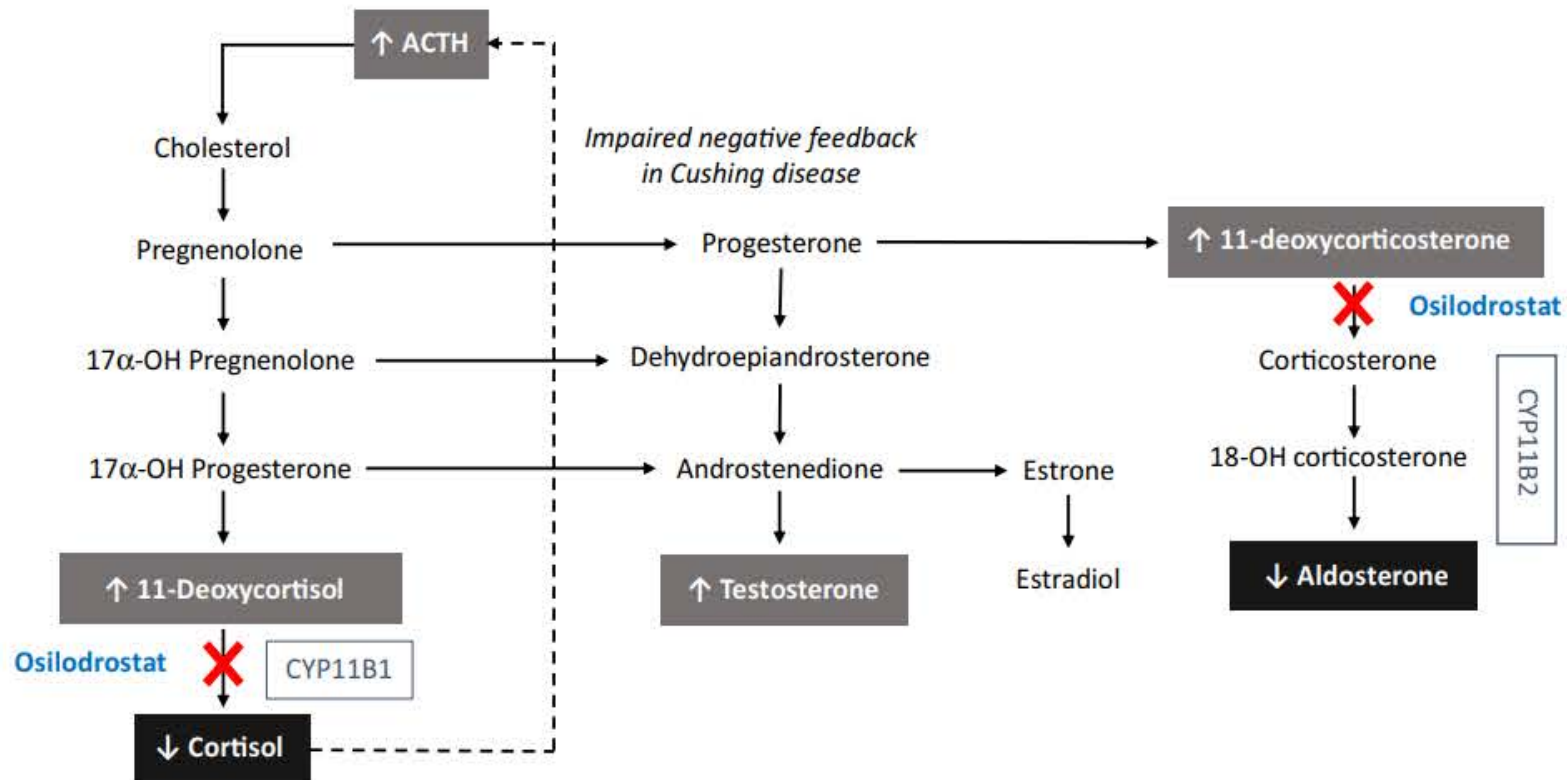


Fig. 1. The site of the action of osilodrostat in the adrenal gland. The dark boxes indicate decreased levels; the gray boxes indicate increased levels. ACTH = adrenocorticotrophic hormone; 17α-OH pregnenolone = 17α-hydroxypregnenolone; 17α-OH progesterone = 17α-hydroxyprogesterone.

Conclusions from Pooled Data

1. Osilodrostat led to sustained mUFC control in all 3 studies.
2. Time to control was shorter in patients with lower BL mUFC values.
3. Median daily osilodrostat dose (6.8 mg) was low but varied widely.
4. Dose titration regimens differed for each study, but AEs were less frequent during long-term treatment than with dose uptitration and were manageable in most without stopping treatment.
5. Personalized therapy during dose titration and lifelong monitoring are needed to optimize clinical outcomes in patients with Cushing's Disease.

Controlled UFC only vs. controlled Late-Night Salivary Cortisol & UFC vs. uncontrolled patients receiving Osilodrostat: Outcomes at 72 weeks

- **Pooled data from LINC III and LINC IV.** Post-hoc analysis comparing long term efficacy in patients with uncontrolled mUFC alone or uncontrolled mean urinary free cortisol (mUFC) and uncontrolled late-night salivary cortisol (LNSC).
- Physical manifestations of hypercortisolism generally improved over the course of the 72-week study, regardless of control of mUFC or LNSC.
- The greatest improvements in cardiovascular/metabolic-related parameters and quality of life were observed in patients with either controlled mUFC and LNSC or controlled mUFC.

	Controlled mUFC and LNSC	Controlled mUFC only	Uncontrolled mUFC and LNSC
Fasting blood glucose	-5.0%	-4.8 %	1.9 %
Hemoglobin A1C	-5.1 %	-4.8%	-1.3%
Weight	-6.5%	-6.5%	-4.5%
Waist circumference	-7.2%	-6.3%	-4.9%

Diagnostic Studies



Is prolactin secretion increased by desmopressin in inferior petrosal sinus sampling (IPSS)?

Background: Previous studies have described an increase in central prolactin (PRL) secretion in response to corticotropin-releasing hormone (CRH) during IPSS in a subset of Cushing's Disease (CD). Desmopressin is used instead of CRH because of availability, but it is unknown whether central PRL secretion also increases after desmopressin as it does after CRH.

Objective: Evaluate the central PRL response to desmopressin administration in patients with ACTH-dependent Cushing's syndrome (CS) undergoing IPSS.

Results: 30 IPSSs performed with desmopressin were included: 24 patients with CD and 6 patients with ectopic ACTH secretion (EAS).

Conclusion: 50% of IPSSs showed a significant central PRL increase after desmopressin in patients with CD, but none in patients with EAS.

- In IPSSs with CRH or CRH + desmopressin, a significant PRL increase was observed in 77.8% of patients with CD, and 2 out of 3 patients with EAS.
- On pathology, there was no correlation with PRL expression on IHC.

Comorbidities



Venous Thromboembolism (VTE) Events: ERCYSYN (The European Registry on Cushing's Syndrome)

- 95 VTE events among 2173 Cushing syndrome patients -prevalence of 4.4 %.
- 57 centers in the database (26 European countries).
- Patients were aged 14-75 years, median age 47 years; 63(66%) were female; 21 (22%) patients were smokers.
- The 95 VTEs : 70 (74%) pituitary-dependent, 12 (13%) adrenal-dependent, 10 (11%) ectopic and 3 (3%) due to other causes.
- Ectopic origin accounted for 10.5% of VTE patients and only 5% of those without VTE.
- Mean \pm SD body mass index (BMI) was 28.8 ± 10.7 kg/m² -more than 3/4 (52; 76%) had a BMI above 25 kg/m² .

Venous Thromboembolism (VTE) Events: ERCYSYN (The European Registry on Cushing's Syndrome)

- **The most frequent comorbidities were hypertension (65 cases, 68%), diabetes mellitus (40, 42%) and osteoporosis (23, 24%).**
- **The VTE group had more surgeries than the no-VTE group. Mean operation rate per patient was 1.42 for the VTE group and 1.2 for no-VTE event group (p=0.006).**

- **VTE is a concern in patients with Cushing's disease.**
- **Obesity and hypertension common comorbidities.**
- **Over half of the VTE events occurred in patients with normocortisolemia.**

Prevalence of Thromboembolic Events in 51 Patients Treated for Cushing's Disease With Pituitary Surgery

- To determine the prevalence of thrombotic events (TE's) in patients with Cushing's Disease undergoing pituitary surgery at University Hospital of Wales.
- 51 Patients (36 females)
 - 5 (9.8 %) had a TE
 - **2 prior to surgery; 3 within 21 days following surgery**

Conclusion

- No correlation between cortisol levels and TE events observed. Timing, dose, and duration of prophylactic anticoagulation needs to be further studied.

	Non VTE (n=46)	VTE (n=5)
mUFC (24h)	662 nmol	1126 nmol
mUFC (24h) at diagnosis	699 nmol	560 nmol
Mean cortisol after overnight DST	327 nmol/L	251 nmol/L
Mean cortisol after overnight DST at diagnosis	321 nmol/L	420 nmol/L
Mean cortisol after surgery	257 nmol/L	221 nmol/L

mUFC –mean urine free cortisol

Quality of Life



Patients vs. Physicians Perspectives

- The Memorial Sloan Kettering (MSK) Pituitary Center established an annual pituitary disease symposium for pituitary patients and health care professionals.
- Surveys at 2020 and 2022 MSK symposia were given to patients and physicians.

	Patients (N=46)	Physicians (N=116)
Patient thought they had no choice in treatment options	21.7%	0.9%
Patient had a lot of hope for improvement	45.7%	71.3%
Patient anxious about their diagnosis	65.2%	94.6%
Patient feeling 'alone' living with disease	60.9%	45.5%
Most common personal goal	Quality of life / mental health	Medical therapies / tumor control
Most perceived unmet need	Education / awareness	Medical therapies / tumor control

Conclusions: Perceptions of this rare disease are dramatically different between patients and physicians.

Clinical Pearls



Clinical Pearls

- Long term use of osilodrostat appears to be safe, effective and well tolerated.
- LINC studies showed the greatest improvements in cardiovascular/metabolic-related parameters and quality of life were observed in patients with either controlled mUFC and LNSC or controlled mUFC.
- Venous thromboembolism present in over 4% of patients in European Registry for Cushing's syndrome. Most were overweight or obese. Another study noted 9.8% of their patients with Cushing's disease had a thromboembolic event.
- Patients' and physicians' perceptions of Cushing's disease and the treatment options available to them are quite different.