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How to manage Cushing's disease after failed primary pituitary surgery

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Invited Review

How to manage Cushing's disease after failed primary pituitary surgery

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Abstract

The first-line treatment for Cushing's disease is transsphenoidal adenomectomy, which can be curative in a significant number of patients. The second-line options in cases of failed primary pituitary surgery include repeat surgery, medical therapy, and radiation. The role for medical therapy has expanded in the last decade, and options include pituitary-targeting drugs, steroid synthesis inhibitors, and glucocorticoid receptor antagonists. Bilateral adrenalectomy is a more aggressive approach, which may be necessary in cases of persistent hypercortisolism despite surgery, medical treatment, or radiation or when rapid normalization of cortisol is needed. We review the available treatment options for Cushing's disease, focusing on the second-line treatment options to consider after failed primary pituitary surgery.

Keywords: manage, Cushing's disease, failed, pituitary, surgeries

Cushing's disease

- In patients with untreated hypercortisolism, mortality rate 4 times higher than general population. causes:
  - metabolic syndrome
  - CVD
  - CHF
  - stroke
  - sepsis
  - thromboembolism causes

- Surgical remission does not eliminate the risk of complications from systemic comorbidities.

- Hypercortisolemia-allied diseases not resolve with the normalization of cortisol levels

Cushing's disease

- some studies have not found high standardized mortality rates (SMRs) in patients with CD in remission.

- several studies have noted increased SMRs:

  multicenter cohort study :patients with CD in remission for at least 10 years and found an SMR for all-cause mortality of 1.61

findings on mortality of CD in remission are inconclusive

- persistent hypercortisolemia is unequivocally a predictor of mortality

- early diagnosis and shortening exposure to hypercortisolism by effective treatment(s) are highly desirable in the management of CD for an overall improved QoL and survival.

Table 1. Selected comorbidities of Cushing's disease and their reversibility after successful treatment.

Comorbidity	Prevalence in CD (%)[1-4]	Persistence of comorbidities after remission
HTN	70-85	• Blood pressure normalizes in 32%-75% CD patients postremission[5-9] • Microvascular remodeling of underlying essential HTN leads to persistence despite remission in others. Increased age, duration of disease, and lower UFC are risk factors for persistence of HTN postremission[7,9,10]
Insulin resistance and impaired glucose tolerance	45-70	• Hyperglycemia may correlate with degree of cortisol elevation, implying that hyperglycemia may remit in patients with higher UFC levels at baseline[7,10] • Insulin resistance may persist after remission, contributing to overall increased cardiovascular mortality in CD
Obesity	70-95	• May remain in the obese category after remission[11,12] • Central adiposity, increased inflammatory markers, and reduced adiponectin are still reported, despite improvement in fat distribution[13] • The underlying inflammation and weight ultimately lead to increased cardiovascular risk in CD
Hypercoagulability	20	• Studies suggest that biochemical remission is not accompanied by normalization of procoagulant or fibrinolytic constraints and patients continue to be at risk for venous thromboemboli[14] • Other studies report an improvement in thrombotic risk 1 year after successful surgery, although larger conclusive studies are lacking[15]
Osteoporosis	50	• Most prominent effect of excess steroids is a decrease in bone formation due to reduced osteoblasts from accelerated apoptosis.[16] Spinal bone loss and subsequent fractures are well described[17,18] • Most studies reveal that cortisol normalization reverse glucocorticoid-induced osteoporosis[19-21] with one concluding th vement is only partial at 2 years[22]

		larger conclusive studies are lacking
Osteoporosis	50	• Most prominent effect of excess steroids is a decrease in bone formation due to reduced osteoblasts from accelerated apoptosis.[16] Spinal bone loss and subsequent fractures are well described[17,18] • Most studies reveal that cortisol normalization reverse glucocorticoid-induced osteoporosis[19-21] with one concluding that the improvement is only partial at 2 years[22] • One study that followed women for a mean of 11 years postremission concluded that while bone formation markers like osteocalcin may improve in patients postremission, overall bone mineral density remained lower than that of the general population,[13] although larger studies are needed to confirm this
Cardiovascular disease	29	• Arterial atherosclerosis is the leading cause of cardiovascular morbidity in patients with CD. Atherosclerosis, HTN, and a prothrombotic diathesis further contribute to overall cardiovascular morbidity • In the evaluation of cardiovascular disease risk, another risk factor recently studied in hypercortisolism is increasing carotid intimal thickness.[23] A prospective study of 25 patients looked at carotid artery thickness in addition to other metabolic markers of atherosclerosis in patients with CD compared with matched controls. Increased cortisol levels lead to a significant increase in carotid intima–media thickness, which is maintained 1 year after remission adding to an overall poor prognostic outcome despite normal cortisol levels[6,24] • In contrast to the vascular system, data on cardiac changes are sparse. Previous studies report abnormal left ventricular remodeling with diastolic dysfunction in untreated hypercortisolism[25,26] • In a prospective study of 15 CD patients and 30 controls done by Feelders *et al.*, normalization of hypercortisolemia led to reversal of left ventricular structural abnormalities[27] • A study by Kamenicky *et al.* also revealed an improvement in ventricular performance and a small increase in left ventricular ejection fraction with remission of CD[28]
Emotional and cognitive changes	70-85	• Emotional lability, depression, and memory impairment lead to a poor quality of life, and even after cure, most of the psychiatric manifestations and cognitive decline are irreversibly impaired[29,30] • Some studies indicate that the prevalence of depression decreases postremission,[31] although Tiemensma *et al.* concluded that patients with CD fare much worse when compared to nonfunctioning adenomas in almost all psychiatric questionnaires for apathy, irritability, depression and anxiety, personality change over a follow-up of 11 years[32]

Selected comorbidities of CD and their reversibility after successful treatment

HTN

- Prevalence in CD (%) :70-85
- Blood pressure normalizes in 32%-75% CD patients postremission
- Microvascular remodeling of underlying essential HTN leads to persistence despite remission in others.
- Increased age, duration of disease, and lower UFC are risk factors for persistence of HTN post remission

Selected comorbidities of CD and their reversibility after successful treatment

- **Insulin resistance and impaired glucose tolerance**
  - Prevalence in CD (%) : 45-70
  - hyperglycemia may remit in patients with higher UFC levels at baseline
  - Insulin resistance may persist after remission, contributing to overall increased cardiovascular mortality in CD

Selected comorbidities of CD and their reversibility after successful treatment

- **Obesity:**
  - 70-95%
  - May remain in the obese category after remission
  - Central adiposity, increased inflammatory markers, and reduced adiponectin are still reported, despite improvement in fat distribution
  - The underlying inflammation and weight ultimately lead to increased cardiovascular risk in CD

Selected comorbidities of CD and their reversibility after successful treatment

- **Hypercoagulability:**
  - 20%
  - Studies suggest biochemical remission is not accompanied by normalization of procoagulant or fibrinolytic constraints and patients continue to be at risk for venous thromboemboli
  - Other studies report an improvement in thrombotic risk 1 year after successful surgery, although larger conclusive studies are lacking.

Selected comorbidities of CD and their reversibility after successful treatment

- **Osteoporosis**
  - 50%
  - Most prominent effect of excess steroids is a decrease in bone formation due to reduced osteoblasts from accelerated apoptosis. Spinal bone loss and subsequent fractures
  - Most studies reveal that cortisol normalization reverse glucocorticoid-induced osteoporosis improvement is only partial at 2 years.
  - One study that followed women for a mean of 11 years post remission concluded that while bone formation markers like osteocalcin may improve in patients postremission, overall bone mineral density remained lower than that of the general population,although larger studies are needed to confirm this

Selected comorbidities of CD and their reversibility after successful treatment

❑ Cardiovascular disease

- 29%
- Arterial atherosclerosis is the leading cause of cardiovascular morbidity in patients with CD.
- Atherosclerosis, HTN, and a prothrombotic diathesis further contribute to overall cardiovascular morbidity
- hypercortisolism is increasing carotid intimal thickness.
- A prospective study Increased cortisol levels lead to a significant increase in carotid intima–media thickness, which is maintained 1 year after remission adding to an overall poor prognostic outcome despite normal cortisol levels.

Selected comorbidities of CD and their reversibility after successful treatment

- **Cardiovascular disease**
  - Previous studies report abnormal left ventricular remodeling with diastolic dysfunction in untreated hypercortisolism
  - In a prospective study normalization of hypercortisolemia led to reversal of left ventricular structural abnormalities
  - A study revealed an improvement in ventricular performance and a small increase in left ventricular ejection fraction with remission of CD.

Selected comorbidities of CD and their reversibility after successful treatment

- **Emotional and cognitive changes**
  - 70-85%
  - Emotional lability, depression, and memory impairment lead to a poor quality of life, and even after cure, most of the psychiatric manifestations and cognitive decline are irreversibly impaired.
  - Some studies indicate that the prevalence of depression decreases postremission.
  - One study concluded that patients with CD fare much worse when compared to nonfunctioning adenomas in almost all psychiatric questionnaires for apathy, irritability depression and anxiety, personality change over a follow-up of 11 years

TREATMENT

- main goals of treatment in CD :
  - eliminate cortisol excess
  - control the tumor
  - maintaining normal pituitary function

TREATMENT

- TSS :
  - Selective adenomectomy is the treatment of choice
  - Subtotal hypophysectomy achieve remission when the tumor is not clearly defined.
  - surgery is not an option:
    - ✓ after failure of primary or second pituitary surgery
    - ✓ patients have a high surgical risk
    - ✓ adenoma has an unfavorable localization

- radiotherapy
- medical therapy
- bilateral adrenalectomy (BLA)

Remission after primary TSS

- postoperative serum cortisol <2 µg/dL
- Three recent systematic meta-analyses found that first- line TSS leads to remission:

  76% - 77.9% - 80%.

- Microadenomas higher remission rates (83%) compared to macroadenomas (68%)
- Remission rate was higher in preoperative and/or intraoperative localization of the adenoma
- Histological confirmation of a corticotroph adenoma has been correlated with a favorable outcome.

Remission after primary TSS

- Postoperative cortisol < 2 µg/dL and ACTH < 5 pg/mL had 100% positive predictive value for remission.
- Delayed remission is likely in postoperative cortisol levels of 2-5 µg/dL,
- cortisol values > 5-10 µg/dL make a delayed remission unlikely.
- Postoperative ACTH-stimulated cortisol levels can also indicate whether biochemical cure has been accomplished.

postoperative low-dose ACTH stimulation test

- indicate whether biochemical cure has been accomplished:
- patients in remission after TSS showed a rapid decrease in cortisol after exogenous ACTH stimulation (<774 nM)
- patients with persistent disease had higher peak cortisol levels (>774 nM).

- explained by: ACTH-receptor downregulation in the adrenal cortex after complete removal of the corticotroph adenoma .
- sensitivity :93% , specificity of 87% in immediate remission of CD after pituitary surgery.
- these cortisol cutoffs have not yet been confirmed in further studies

Remission after primary TSS

- neurosurgeon's skills and experience to influence outcomes and remission states after TSS.
- 5-fold larger hospital caseload was associated with better outcome
- 5-fold higher caseload of the performing neurosurgeon was also associated with significantly better outcomes
- Postoperative complication rates lower in high-volume hospitals and high-volume surgeons, particularly fluid disturbances, and DI.
- lowest complication rates in neurosurgeons who have performed more than 200 TSS.

Remission after primary TSS

A meta-analysis involving in total > 6600 patients :

- microadenomas :similar remission rates for both microscopic and endoscopic surgeries
- Macroadenomas: higher remission (76.3% vs 59.9%) and lower recurrence (1.5% vs 17.0%) rates when using the endoscopic vs microscopic approach
- possible explanation :higher flexibility when using endoscopic technique for large, extensive macroadenomas.

Failed Surgery

Secondary TSS

-Remission rates for repeat surgery vary between 45.5% and 83%
- Microadenomas have lower recurrence rates after repeat TSS compared to macroadenomas
- Postoperative serum cortisol levels < 2ug/dl is a predictor for remission after repeat TSS
- Complications following repeat TSS seem to vary with the aggressiveness of the applied surgical technique

RADIATION

- No association between the use of concomitant anti-cortisolemic drugs at the time of radiation and remission (162)
- Tumor volume shown to be higher in the uncured group than in the remission group (172)
- No significant relationship between remission and tumor extension, maximum or margin dose, or treatment isodose (173)

MEDICATIONS

- Drugs to treat Cushing's Disease include pituitary targeted drugs, adrenal steroidogenesis inhibitors and glucocorticoid receptor antagonists
- Medical therapy to should be tailored to the patient based on patient characteristics, drug features, availability and cost

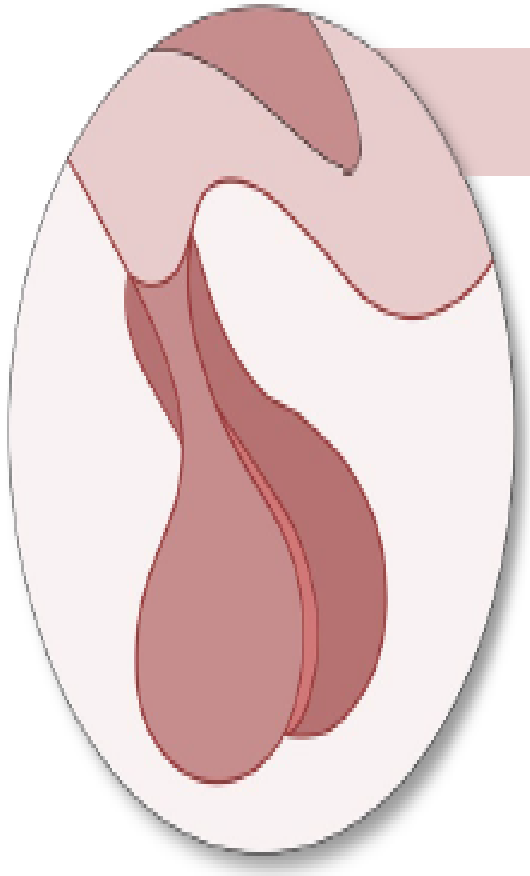
BLA

- Often considered a last resort treatment or when other options are not available specially in women desiring pregnancy
- Consider BLA for severe hypercortisolemia with associated complications

TREATMENT

The decision on the second-line treatment:

- age
- Comorbidities
- extent and invasiveness of the residual tumor
- risk of hypopituitarism, especially in young, premenopausal females, who might plan a future pregnancy.



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Repeat TSS

- repeat TSS effective treatment option after failed primary TSS to achieve long-term remission.

- A recently published meta-analysis found:

  - remission rates of 80% for primary and 58% for repeat surgery
  - this meta-analysis included studies on patients with persistent but also with recurrent CD

Repeat TSS

- In case series including only persistent CD:
  - remission rates for repeat TSS :vary between 45.5%- 83%
  - remission rates for primary TSs: 69.3%- 84.3%.
  - Higher remission rates are also achieved in pituitary centers with highly experienced, large-volume neurosurgeons.

surgical techniques seem more aggressive for repeat TSS in some series.

Repeat TSS

optimal timing of the second surgical intervention is still not clear.

- early :within days up to 4 weeks
  - reoperation in unequivocal pituitary origin of CD
  - absence of scar tissue and the preservation of anatomical landmarks might improve surgical outcome.
- delaye:
  - avoid unnecessary reoperations, due to reported delayed remissions in 6% of the patients.

Endocrine Consensus Statement recommends:

ideal time for repeat TSS for residual disease is when active, persistent disease is confirmed.

a delay of 4-6 weeks is acceptable to avoid unnecessary reoperations

Repeat TSS

Recurrence

- after repeat surgery for CD has been reported in 2 series:5.6%,33%
- These rates related with :

✓ the longer follow-up periods of the patients

✓ with the variable criteria for recurrence

✓ cases with more aggressive tumor behavior

- recurrence rate is higher in macroadenomas(45%) compared to microadenomas (19%)

Predictors of remission after repeat TSS

- Remission rates in microadenoma undergoing selective adenomectomy :65% -90%.
- Surgical success rates are lower in invasive macroadenomas.
- predictors of surgical outcomes:

- ✓ the number of pituitary surgeries
- ✓ duration of disease
- ✓ tumor size
- ✓ hypocortisolism is an indicator of surgical remission:

After repeat TSS, cortisol values < 2 µg/dL have been associated with higher remission rates whereas data on ACTH values after repeat TSS are lacking.

- In contrast to primary surgery, tumor identification on MRI has not been found to be a predictor
- Recurrent CD as an indication for repeat TSS has a significantly higher remission rate (80%)compared to persistent disease (54%)

Complications associated with repeat TSS

- mortality very low :
  - mortality rate was higher in repeat surgery (1.5%)compared to primary surgery (0.4%) ,this meta- analysis included older studies.
  - Reported mortality after repeat TSS is very low in series of the last 20 years,(0%).

- postoperative complications :

higher after repeat TSS compared to primary surgery although the difference was not significant.

  - Hypopituitarism
  - CSF leak
  - Ttransient DI
  - high risk on thromboembolic complications in the first months after pituitary surgery

(whether thromboembolic complications occur more often after repeat TSS compared to primary TTS has not been investigated.)

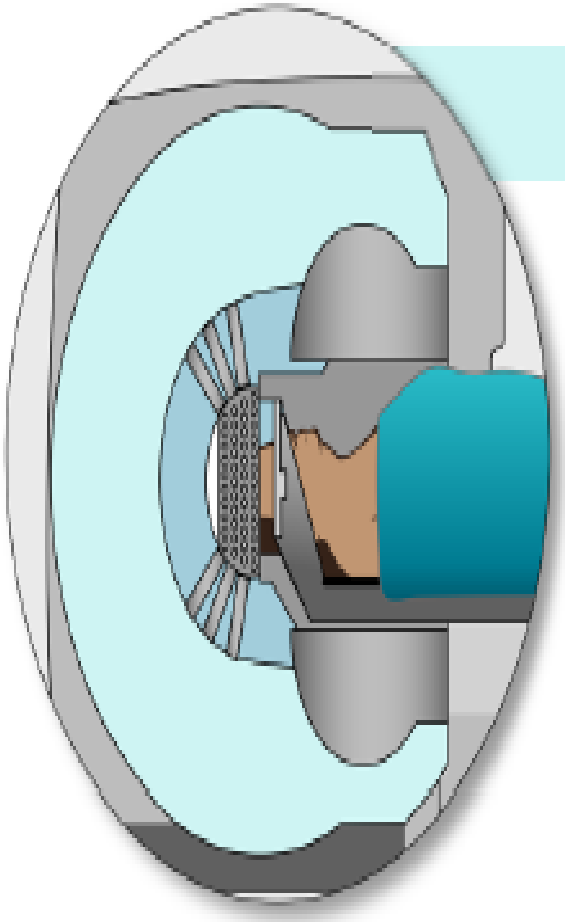
Potential approaches to improve outcome after repeat TSS

- improve imaging modalities:

- . Ultrahigh-field MRI, with strengths of 7 T or higher, increase the detection rate for microadenomas.
- 7 T MRI, not all suspected adenomas were confirmed to be corticotroph tumors in subsequent histology
- risk of identifying higher number of incidental lesions.

Potential approaches to improve outcome after repeat TSS

- Molecular imaging
- localizing corticotroph adenomas in cases MRI scans are indeterminate or negative.
- 11C-Methionine PET have proven effective in identifying ACTH-secreting adenomas in both newly diagnosed and recurrent Cushing's disease)
- 18F-FDG PET with CRH stimulation improving detection rates for 18F-FDG PET
- 68Ga CRH PET-CT(a noninvasive molecular imaging modality, targeting CRH receptors,) , successfully identified pituitary adenomas (including those <6 mm)



RADIATION

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Radiotherapy

- second- or third-line option for CD and offers sustained biochemical remission in most cases.
- Most studies did not distinguish between persistent and recurrent CD

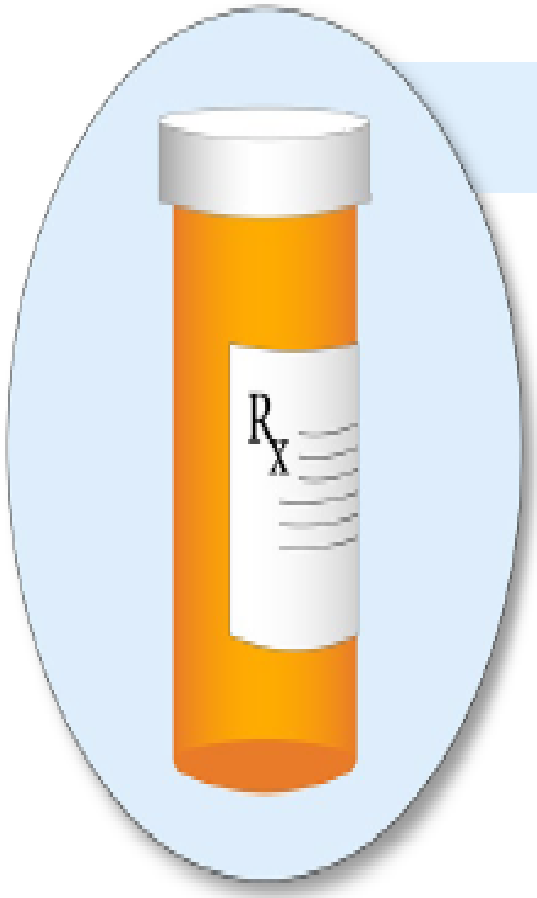
- Gamma Knife radiosurgery (GKRS) was the most well-established means of stereotactic radiosurgery (SRS):

  - Biochemical remission rates post-SRS: 50%-65%
  - radiological tumor control :90%
  - maximum efficacy at the end of 3-4 years.
  - The use of medical treatment to normalize hypercortisolemia prior to radiotherapy did not result in higher remission.

Radiotherapy

- The main adverse effects:

  - hypopituitarism (35%-60% of patients at 5 years)
  - optic neuropathy (1%-2%),
  - other cranial neuropathies (2%-4%),
  - with rarer ones being secondary brain tumors



MEDICATIONS

- Drugs to treat Cushing's Disease include pituitary targeted drugs, adrenal steroidogenesis inhibitors and glucocorticoid receptor antagonists
- Medical therapy to should be tailored to the patient based on patient characteristics, drug features, availability and cost

Medical therapy

- Potential indications :
  - failed pituitary surgery
  - a high surgical risk due to age or serious comorbidities
  - to bridge the period until radiotherapy becomes effective
  - acute complications of severe cortisol excess (eg, psychosis)
  - pretreatment before pituitary surgery

- Medical therapy categorized into 3 groups:
  - pituitary-targeting drugs
  - steroid synthesis inhibitors
  - glucocorticoid receptor (GR) antagonists.

Medical therapy

- **pasireotide and osilodrostat** are approved FDA and EMA for use in CD and CS who have failed surgery or are poor surgical candidates.

- **Mifepristone and levoketoconazole** are FDA-approved medications for endogenous hyper cortisolemia secondary to CS.

- **Ketoconazole and metyrapone** are officially approved for use by the EMA but are used off label in the United States.

- **Cabergoline** is used off label.

Medical therapy

- choice of medical (combination) treatment should be made on an individual basis integrating patient characteristics:
  - severity of hypercortisolism
  - need for tumor growth control
  - drug characteristics (onset of action and potential side effects in the individual patient)
  - availability
  - Costs.

- Normalization of UFC alone not be a completely reliable marker of drug efficacy, and multiple serial tests combining UFC and late-night salivary cortisol (LNSC) are recommended to monitor outcomes.

Medical therapy

- A recent study has shown that patients treated with cortisol-lowering drugs and normal UFC still maintained a mild state of hypercortisolism compared to patients with successful pituitary surgery or after BLA :

medical treatment long term might not be as effective as a successful pituitary surgery or BLA, despite normal UFC

- discontinuation rate of drug is high:
  - only 38% of the patients achieve long-term control.
  - alternative therapeutic options such as repeat TSS, radiotherapy, and BLA should be evaluated carefully in patients with long-term drug therapy.

Pituitary-targeting drugs

- Corticotroph tumor cells highly express SRS5 and dopamine receptor subtype 2. Suppress ACTH production by the corticotroph adenoma :include pasireotide and cabergoline:

somatostatin receptor analog :

- **Pasireotide**: .

1. universal pasireotide, in sc formulation administrated bid, control cortisol production 26%-35% of patien
2. Long-acting pasireotide once monthly, leads to normalization of UFC in 40% of patients,an effective response rate in mildly elevated baseline UFC, as well as in higher baseline UFC levels.

- **asireotide** :effective in mild hypercortisolism

pasireotide

- short- and long-acting **pasireotide**, corticotroph tumor shrinkage:

useful in the preoperative setting and to control tumor growth of (expanding) macroadenomas if surgery is not an option.

- Hyperglycemia:
  - most common side effect : 50% (DM: 24%)
  - caused by inhibition of postprandial incretin release
  - treatment with metformin and/or GLP-1-based therapy (DDP-4 inhibitor and GLP-1 receptor agonist) is recommended.

Cabergoline

- off label to treat CD.
- efficacy with cabergoline, (0.5-7.0 mg / w): 25% -40%,
- prospective study showed a very limited efficacy of cabergoline (2.5-5 mg /W) although the treatment period (6 weeks) was relatively short.
- Main adverse events :headache, dizziness, nausea, and addictive/compulsive behavior.

Pituitary-targeting drugs

- **Pasireotide and cabergoline :**

  additive or synergistic effects, starting with pasireotide monotherapy, addition of cabergoline to pasireotide doubled the number of patients in whom cortisol production could be fully controlled.

- **pasireotide–cabergoline -ketoconazole**:

  addition of low-dose ketoconazole increased biochemical remission rate to 90%, although this was investigated in a very small cohort of patients.

Medical therapy

Temozolomide

- chemotherapeutic drug treat aggressive corticotroph tumors and Nelson tumors.
- Temozolomide can induce tumor shrinkage via activation of apoptosis.
- It is reasonably well tolerated; most common adverse events are nausea, vomiting, and bone marrow depression.

Steroid synthesis inhibitors

- **Metyrapone** and **ketoconazole:**
  - retrospective studies : similar efficacy of 50%-70% for normalization of cortisol production.
  - real efficacy of both drugs may be lower due to selection bias.

- side effects of **metyrapone** :
  - gastrointestinal upset
  - Nausea
  - worsening of hypertension
  - hypokalemia
  - hirsutism due to increased adrenal mineralocorticoid precursor and androgen production

Steroid synthesis inhibitors

side effects of **ketoconazole** :

- GI complaints
- hepatotoxicity:
  - primary concern in 15% of patients
  - mandating careful monitoring of hepatic enzymes.
  - not dose dependent.
  - asymptomatic
  - effects reversible upon drug withdrawal
  - varies from mild to serious life-threatening hepatitis
  - male hypogonadism.

Steroid synthesis inhibitors

- **Etomidate**
  - anesthetic drug
  - rapidly block adrenal steroidogenesis
  - used in lower doses in severe complicated hypercortisolism in ICU

Steroid synthesis inhibitors

- **osilodrostat**
  - inhibitor of the steroidogenic enzymes CYP11B1 and CYP11B2

- **levoketoconazole**

osilodrostat

In 2 large prospective studies LINC-3and LINC-4, osilodrostat was shown to be a potent inhibitor of cortisol synthesis.

- In LINC-3: 86% on osilodrostat maintained normal UFC
- In LINC-4 :77% patients with CD, complete normalization of UFC
- LINC-3 and LINC-4:
  - improvement of physical features, cardiovascular/metabolic parameters, and QoL.
  - osilodrostat monotherapy can control cortisol production in ectopic ACTH production

osilodrostat

- side effects :
  - hypocortisolism- related adverse events :adrenal insufficiency
  - accumulation of mineralocorticoid precursors: HTN and hypokalemia
  - accumulation of androgens :hirsutism

Levoketoconazole

- a single 2S,4R enantiomer of racemic ketoconazole.
- FDA approved in the United States for the treatment of CS with failed surgical remission or in patients where surgery is not a viable option.
- inhibit CYP11B1, CYP17A1, and CYP21A2 enzymes
- 15- to 25-fold more potently compared to ketoconazole
- *in vivo* animal studies reveal less potent inhibition of CYP7A which protects against cholestasis and hepatotoxicity.this needs validation in future studies.
- a prospective study in 94 CS patients with levoketoconazole:
  - 62% had a complete biochemical response at the end of the 6-month maintenance phase
  - improvements of clinical symptoms, cardiovascular risk factors, and QoL.

GR antagonists

mifepristone

- GR and progestron antagonist
- improve regulation of BP and DM in patients with CS.

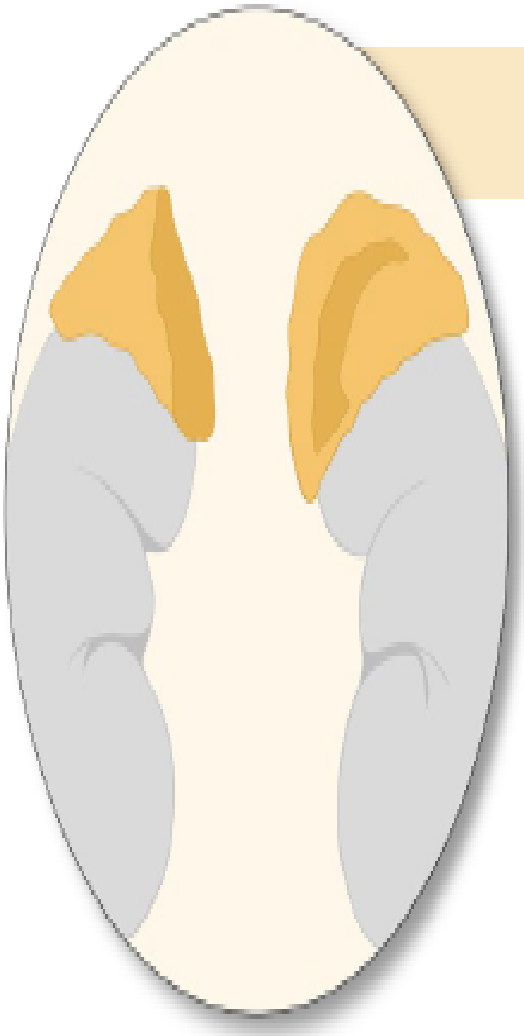
- rapid onset of action and use to treat patients with acute complications:
  - psychosis
  - severe hypercortisolism.

- side effects:
  - vaginal bleeding
  - endometrial thickening based on its anti progestin action
  - stimulation of the mineralocorticoid receptors leading to: hypokalemia, edema, and increased BP.

GR antagonists

Relacorilant

- selective GR antagonist
- improve HTN and glycemic parameters
- In contrast to mifepristone, induced only a small increase in ACTH and UFC levels, which was not accompanied by mineralocorticoid adverse events
- suitable for long-term use
- A large prospective study with relacorilant is currently being conducted (GRACE study)



BLA

- Often considered a last resort treatment or when other options are not available specially in women desiring pregnancy
- Consider BLA for severe hypercortisolemia with associated complications

BLA

- BLA is an aggressive but rather unavoidable option in:

  - persistence of disease despite surgery, medical treatment, or radiation
  - rapid normalization of cortisol is indicated.

- A meta-analysis on BLA of 37 studies (1320 patients, 82% with CD) showed partial or full remission of signs and symptoms

  - improvement in muscular weakness: 93%
  - menstrual cycle irregularities : 75%
  - overall fatigue :70%
  - HTN :82%
  - DM: 70%
  - surgery-related 30-day mortality 0% - 15% (median 3%).

- Postoperative care with attention to anticoagulation and mobility are key.

BLA

- most studies have found significant improvement in QoL after BLA in patients with CD.

  - A retrospective study looked at QoL surveys completed by 40 patients with a follow-up of 5 years and demonstrated:

    86% :felt good to excellent compared with 1-year pre-BLA,

    46% :fatigue.

  - Oswald *et al showed* QoL remained impaired in 45.0% of female and 16.7% of male patients despite remission.

some data are conflicting, overall results are positive

BLA

- After BLA, patients are started on life-long glucocorticoid and mineralocorticoid replacement therapy with close clinical follow-up.
- As adrenal crises can be precipitated by infections, trauma, or stress after BLA, careful education and instruction of patients and their relatives is crucial.
- The median number of adrenal crises per 100 patient-years has been reported as 4 by Oswald *et al.* and 9.3 (6 studies, 203 patients) by Ritzel *et al.*

BLA

- Nelson's syndrome or corticotroph tumor progression occur after BLA and is associated with increased ACTH levels and corticotroph tumor enlargement.
- Loss of feedback inhibition of HPA axis leads cutaneous hyperpigmentation.
- Tumor progression on MRI or new pituitary tumor after BLA along with hyperpigmentation and progressive increase in ACTH levels maybe suspicious for NS.
- Treatment options for NS include pituitary surgery and radiation therapy ,temozolomide

- Treatment of CD challenging .
- ultimate treatment goal to fully control cortisol production, in order to reverse morbidity and mortality and to improve QoL.
- Pituitary surgery is the first-line treatment modality of CD
- patients with long-term medical treatment, a repeat TTS should always be considered when the patient has a reasonable chance of being in remission.
- management CD after failed pituitary surgery should be performed by a multidisciplinary team with a tailor-made approach coupling the optimal second-line treatment modality to the individual patient since each treatment modality has its own advantages and limitations, but none is clearly superior to others

THANK YOU FOR ATTENTION