Pharmacologic and radiant treatments: to whom, when, how

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AZIENDA OSPEDALIERA SANT' ANDREA

Conflicts of interest

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

nessuno / none

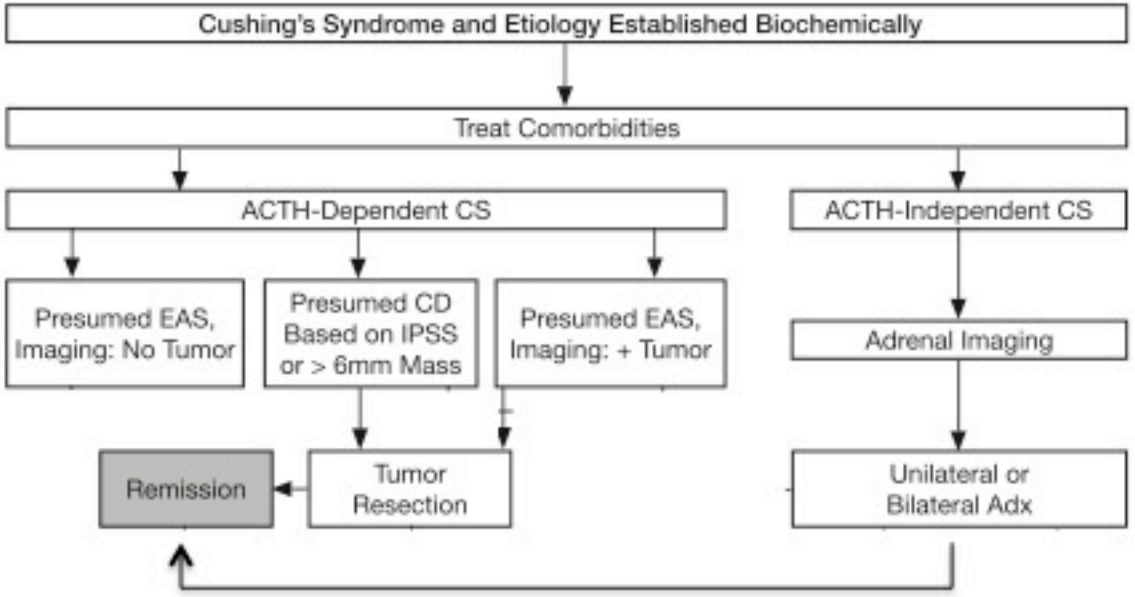
Drugs & Ionizing radiations:

Museum of modern art, DC

- To whom
- When
- How

Cushing's care: therapy of choice

Surgery is the first-line approach



J Clin Endocrinol Metab, 2015, 100(8):2807–2831 modified

Drugs & Ionizing radiations

Phillips collection, DC

Pharmacological treatment

Pharmacological treatment

To Whom and When pharmacological treatment

SPECIAL FEATURE

Clinical Practice Guideline

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, and Antoine Tabarin

J Clin Endocrinol Metab, 2015, 100(8):2807–2831

First-line approach

✧ Occult or metastatic ectopic ACTH-secretion (EAS)

To Whom and When pharmacological treatment

Second-line approach

- ✧ Inefficacy of selective adenomectomy (10-50%) (TTS) with or without radiotherapy (RT)

Nieman LK et al

J Clin Endocrinol Metab, 2015, 100(8):2807–2831

To Whom and When pharmacological treatment

Additional treatment

✧ Adrenocortical carcinoma (ACC)

Nieman LK et al

J Clin Endocrinol Metab, 2015, 100(8):2807–2831

To Whom and **When** pharmacological treatment

- Not for surgical candidates or patients with persistent Cushing's disease (CD) after TTS

Nieman LK et al

J Clin Endocrinol Metab, 2015, 100(8):2807–2831

When pharmacological treatment

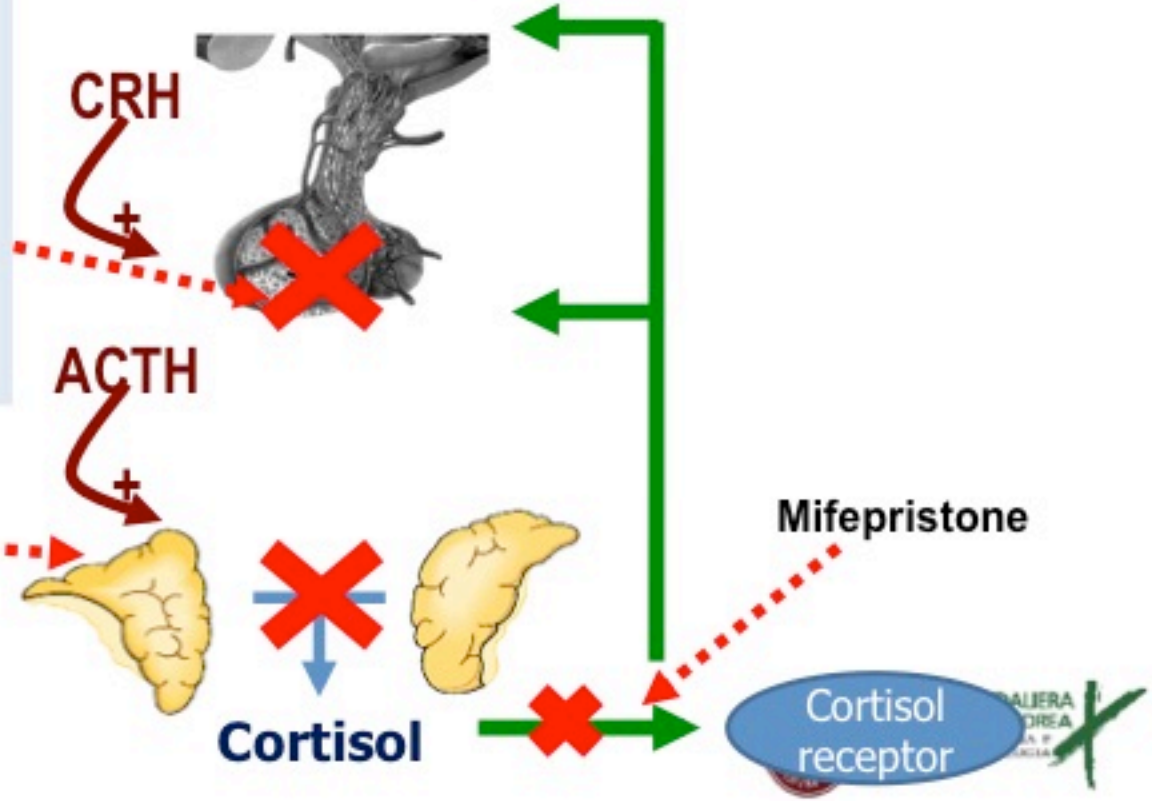
When the target is not clear or missing

When there is no option for other therapies

Drug tested in Cushing

- Somatostatin analogs
- Dopamine agonists
- Somatostatin-dopamin chimeric compounds
- PPAR-γ ligands
- Retinoic acid receptor agonists
- EGFR blockers
- CDK inhibitors
- HSP90 inhibitors
- Alkylating chemoterapeutic agents

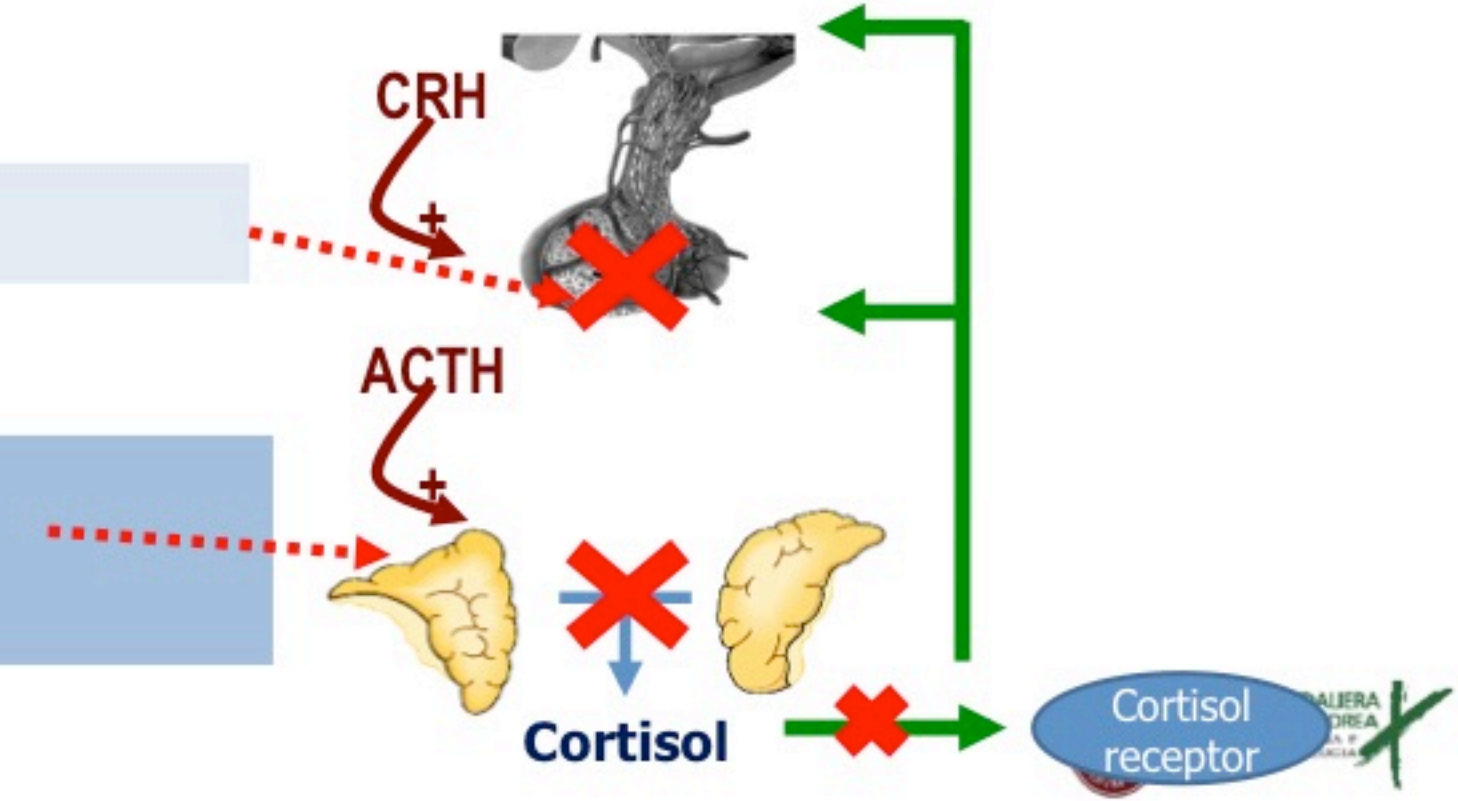
- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate
- Aminoglutethimide
- Trilostane
- LCI699
- ATR-101
- GPS1573
- GPS1574



How: therapeutic options available

- Pasireotide

- Ketoconazole
- Metyrapone
- Mitotane



www.associazionemediciendocrinologi.it

ame flash

nr. 15/1 - settembre 2015

ITALIAN EXPERT POSITION SULLA TERAPIA MEDICA NELLA SINDROME DI CUSHING (forme ACTH-dipendenti e ACTH-indipendenti)

Responsabile Editoriale
Renato Cozzi

Vincenzo Toscano[1] (vincenzo.toscano@ospedalesantandrea.it), **Massimo Terzolo**[2], **Massimo Mannelli**[3], **Marco Boscaro**[4], **Francesca Pecori Giraldi**[5], **Antonio Stigliano**[1]

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[2]Divisione di Medicina Interna I, Ospedale San Luigi, Orbassano, Università di Torino
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[4]Endocrinologia, Dipartimento di Medicina DIMED, Ospedale Universitario di Padova
[5]Dipartimento di Scienze Cliniche e di Salute Comunitaria, Università di Milano

To Whom and When pharmacological treatment

- ✧ Surgery refusal or patients cannot undergo radiant therapy
- ✧ Surgery preparation
- ✧ Acute complications of severe hypercortisolism

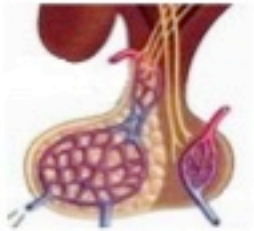
How: therapeutic goals

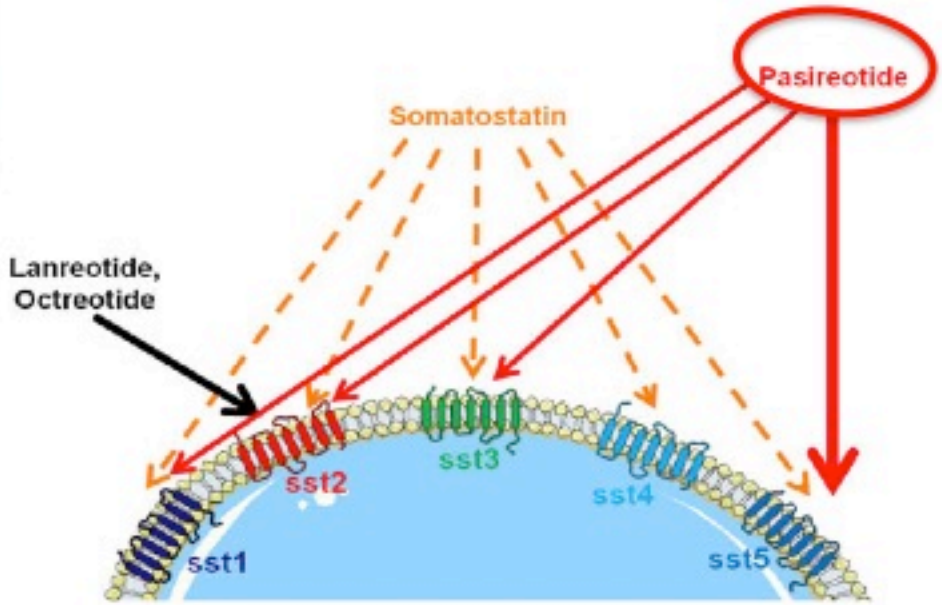
- ✧ Normalization of biochemical parameters
- ✧ Reversibility of clinical picture
- ✧ Morbidity reduction
- ✧ Control of disease

Central drug

Museum of modern art, DC

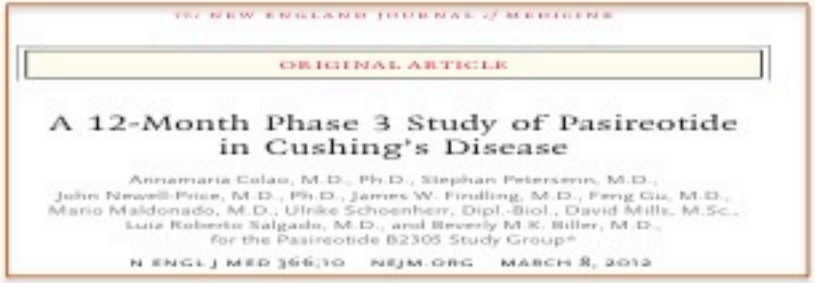
Ligands of somatostatin receptors





Fleseriu M & Petersen S, Pituitary '12

Pasireotide



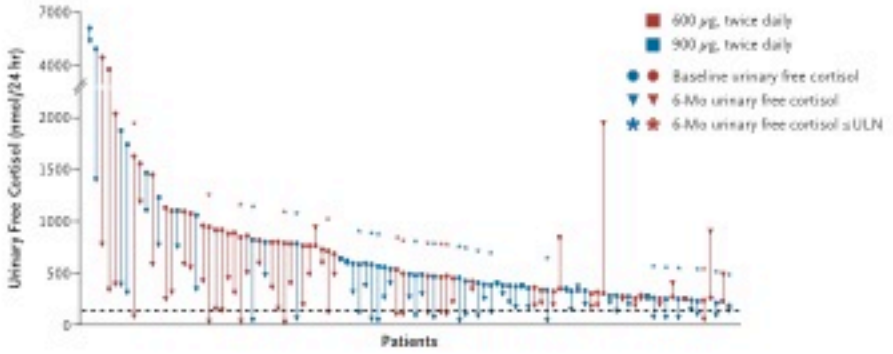
THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

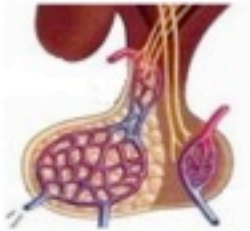
Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D., for the Pasireotide B2305 Study Group*

N ENGL J MED 366;10 NEJM.ORG MARCH 8, 2012



- ✧ 600 or 900 mg sc twice daily
- ✧ 20% of 162 patients (UFC average on 4 collection ≥1.5xULN) treated normalized UFC after 6 months
- ✧ Improvement of blood pressure, lipidic profile, weight, HRQOL
- ✧ Tumor volume reduction in 44% of patients (900 mg)

Pasireotide



Indication (when): Treatment of adult patients with CD when surgery is not indicated or ineffective

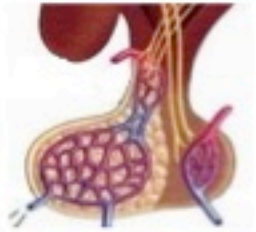
Administration (how): 0.3 - 0.6 – 0.9 mg subcutaneously twice daily

Pasireotide: how

- Initial dose: 0.6 mg sc twice daily
- First evaluation: after 2 months
- Dosage increase: 0.9 mg based on response to therapy (only if 0.6 mg dose it was well tolerated)
- Dosage reduction: 0.3 mg twice a day in case of side effects

Pasireotide: from experience to clinical practice

Warning:

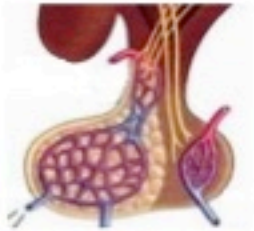


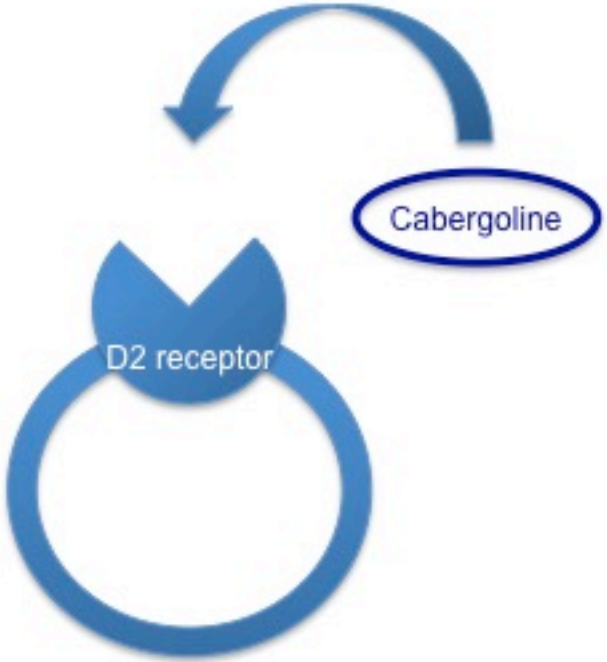
- blood glucose monitoring
- cholelithiasis: liver ultrasound before and during therapy
- liver function before and after treatment
- control QT length to ECG
- cortisol assay for hypocortisolism risk
- pituitary hormones assay, FT4, GH/IGF-I before and during treatment

Drug potentially used in Cushing's treatment

* In case of refuse or no other therapeutic possibilities

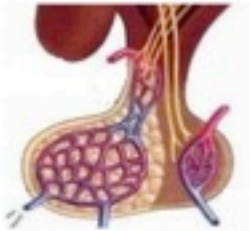
Dopamine agonist





Ciato D et al, Exp Opin Invest Drugs ' 17

Cabergoline

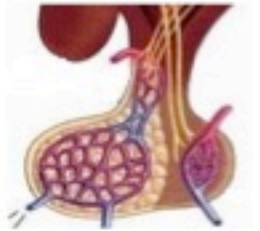


Indication (when): Treatment of adult patients with unsuccessful surgery for CD

Administration (how): 1-7 mg week

Pivonello R et al JCEM '09
Godbout A et al Eur J End '10

Alkylating chemotherapeutic agents



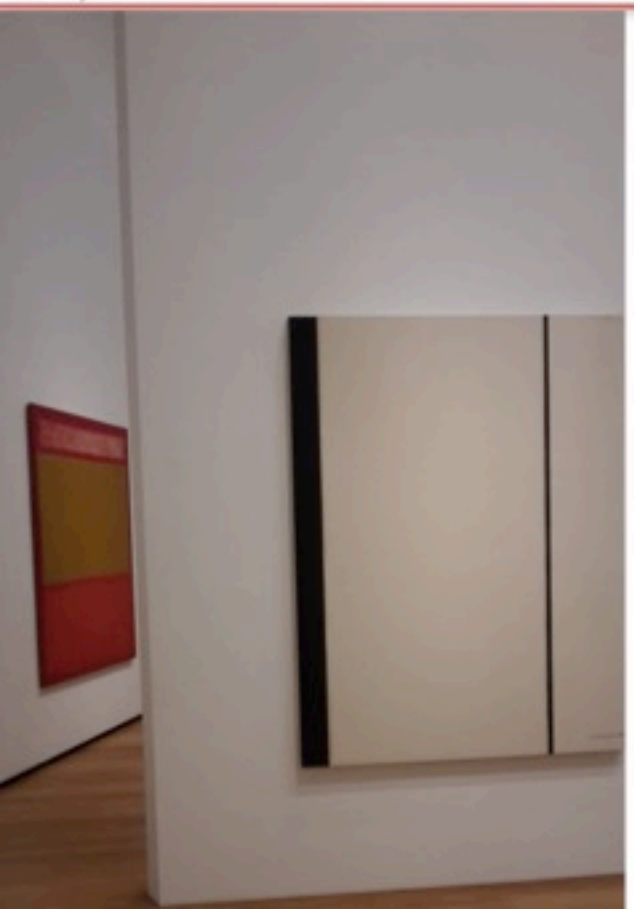
Temozolomide used in malignant brain tumor

Indication (when): Treatment of aggressive corticotroph tumors: response rate 50%

Administration (how): 150-200 mg/m^2/day every 28 days

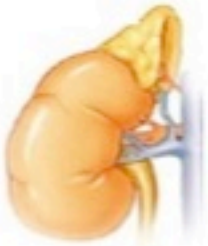
Lasolle H et al Eur J End '17
Halevy C & Withelaw BC, Pituitary '17

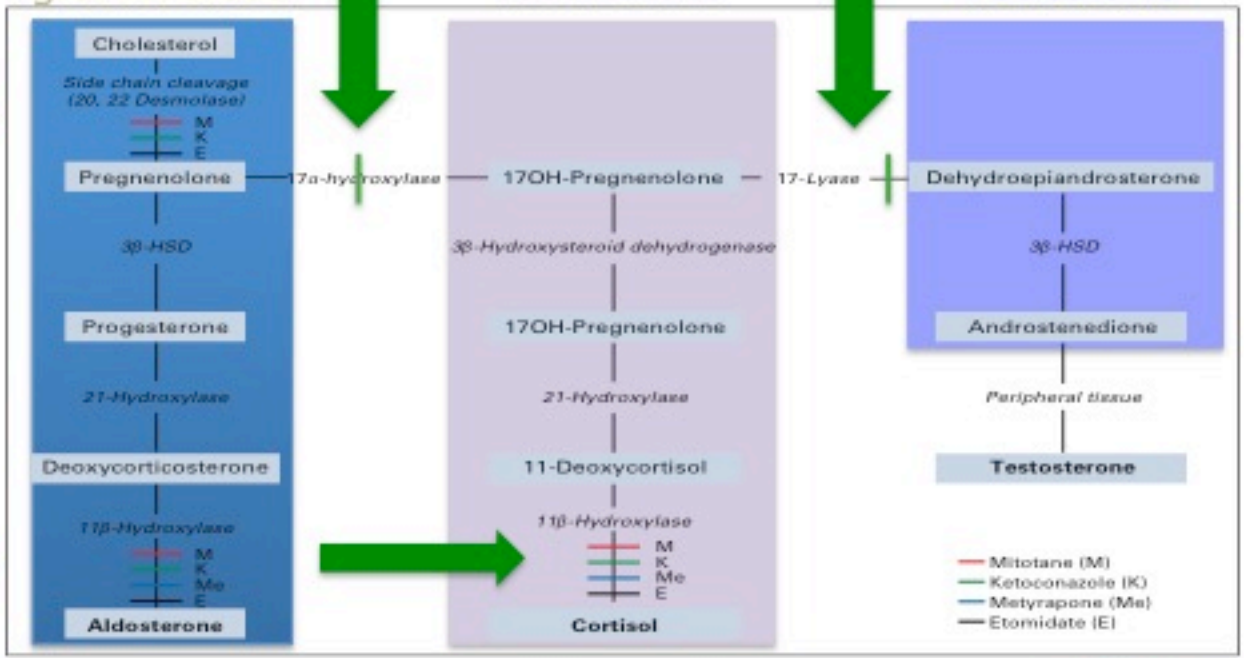
Peripheral drugs



Museum of modern art, DC

Ketoconazole





Veytsman I mod, JCO '09

Ketoconazole in Cushing's Disease: Is It Worth a Try?

Frederic Castinetti, Laurence Guignat, Pauline Giraud, Marie Muller, Peter Kamenicky, Delphine Drui, Philippe Caron, Fiorina Luca, Bruno Donadille, Marie Christine Vantyghem, Helene Bihan, Brigitte Delemer, Gerald Raverot, Emmanuelle Motte, Melanie Philippon, Isabelle Morange, Bernard Conte-Devolx, Laurent Quinquis, Monique Martinie, Delphine Vezzosi, Maelle Le Bras, Camille Baudry, Sophie Christin-Maitre, Bernard Goichot, Philippe Chanson, Jacques Young, Olivier Chabre, Antoine Tabarin, Jerome Bertherat, and Thierry Brue JCEM 2014

12 years of clinical experience from several French centers

200 patients

40 as a presurgical treatment

Antisecretory efficacy (n=39)
- 19 Controlled (48.7%)
- 14 Partially controlled (35.6%)
- 6 Uncontrolled (15.4%)

	Initial	Improved
Clinical signs	38	42.1%
Hypertension	26	50%
Hypokalemia	13	38.4%
Diabetes	16	50%

32 as a primary treatment (CI or refusal to surgery)

Antisecretory efficacy (n=32)
- 16 Controlled (50%)
- 9 Partially controlled (28.1%)
- 7 Uncontrolled (21.8%)

	Initial	Improved
Clinical signs	28	67.8%
Hypertension	23	34.8%
Hypokalemia	7	28.6%
Diabetes	12	58.3%

128 as a secondary treatment
- Unsuccesful surgery (n=93)
- Following radiotherapy (n=35)

Antisecretory efficacy (n=126)
- 62 Controlled (49.2%)
- 28 Partially controlled (22.2%)
- 36 Uncontrolled (28.5%)

	Initial	Improved
Clinical signs	106	50%
Hypertension	67	41.8%
Hypokalemia	19	42.1%
Diabetes	27	59.2%

Tolerance data in 190 patients

- 25% obtained a UFC reduction at least 50%
- 49% normalize UFC at last follow up
- Different response based on baseline UFC value

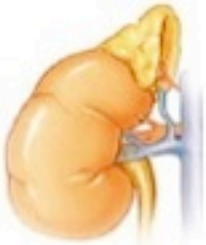
Ketoconazole: safety profile

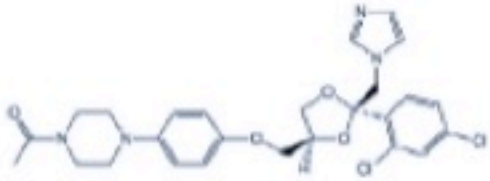
Table 3. Adverse Effects Induced by Ketoconazole[a]

	Frequency	Mean Dose (mg/d)	Min–Max
Liver enzyme increase	30 (15.8%)	772.4 ± 305.7	400–1200
Gastrointestinal complaints	25 (13.1%)	625 ± 258.3	400–1200
Adrenal insufficiency	10 (5.4%)	700 ± 256	400–1200
Pruritus	7 (3.7%)	700 ± 385.6	400–1200
Intense fatigue	2 (1.25%)	700	600–800
Hair loss	2 (1.25%)	700	600–800
Leg edema	2 (1.25%)	800	800–800
Muscle pain	2 (1.25%)	700	200–1200
Dyspnea	1 (0.6%)	400	400
Hypertriglyceridemia	1 (0.6%)	800	800
Leukoneutropenia	1 (0.6%)	600	600
Dizziness	1 (0.6%)	1200	1200
Increased creatinine level	1 (0.6%)	600	600

Castinetti F, JCEM 2014

Ketoconazole





Indications (when): treatment of endogenous hypercortisolism in adults or children

Pharmaceutical preparation (how): tablets 200 mg

Ketoconazole: how

- **Starting treatment:** 400–600 mg fractionated in two or three doses daily

- **Administration:** individual tritation up to 800 -1200 mg fractionated in two or three doses daily

Ketoconazole: from experience to clinical practice

✧ Precautions:

- check liver function before and periodically during treatment
- drug discontinuation when increasing liver enzymes ≥ 3 times the normal range
- effect on gonadal testosterone synthesis
- avoid concomitant administration of proton-pump inhibitors
- CYP3A4 inhibitor
- escape in 10-15% (cortisol monitoring)

Ketoconazole: from experience to clinical practice

- Adrenal function monitoring: within one week of starting treatment and periodically
- Monitoring ECG: QT interval control within one week of starting treatment treatment and periodically
- Absolute contraindications: pregnancy or in women of childbearing age who do not use contraceptive

Drug potentially used in Cushing's treatment

		Cushing patients	Irsutism female	Liver damage	Severe CD/CS	Pregnancy	Pediatrics
PRE-SURGERY	EAS	■	■		■		
	CD	■	■		■		
	CS	■	■		■		
POST-SURGERY	EAS	■	■		■		
	CD				■		
	CS	■	■		■		
MEDICAL TERAPY ONLY*	EAS	■	■		■		
	CD				■		
	CS	■	■		■		

■ Keto/Mety

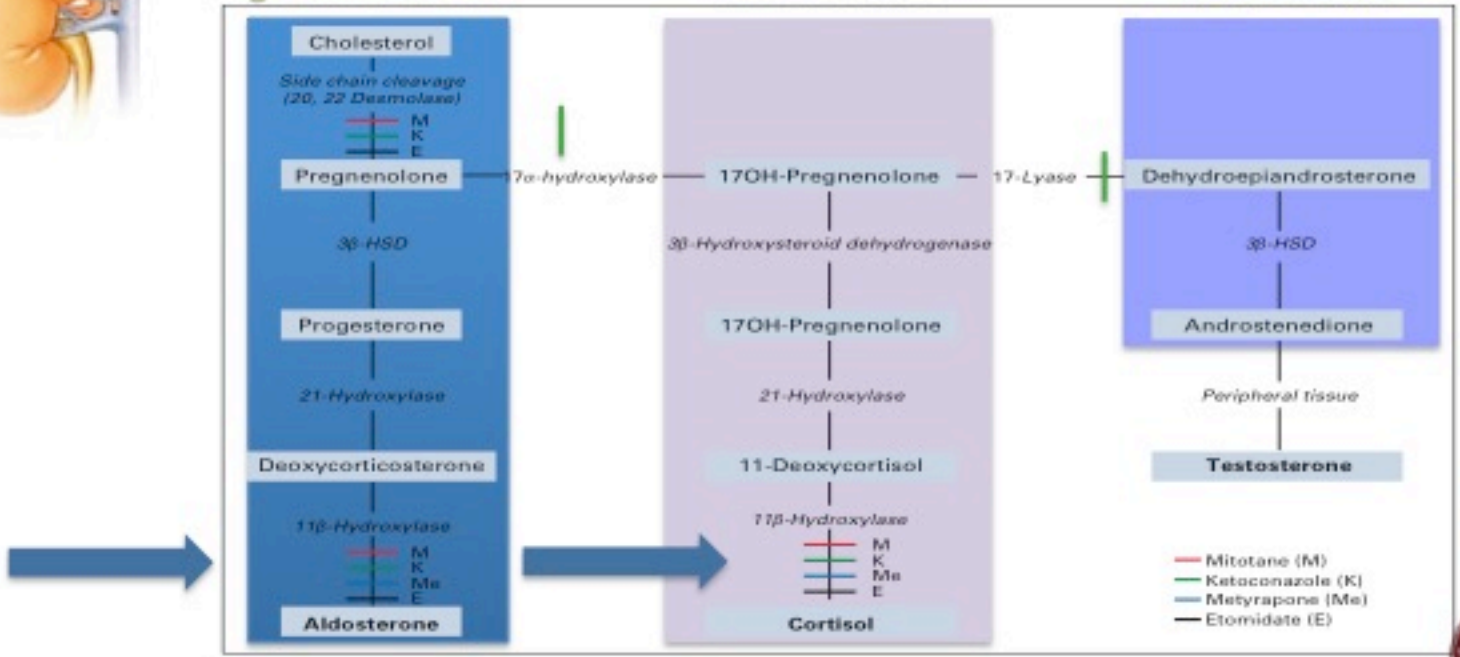
■ Pasireotide

■ Keto conazole

■ Metyrapone

* In case of refuse or no other therapeutic possibilities

Metyrapone



Veytsman I mod, JCO '09

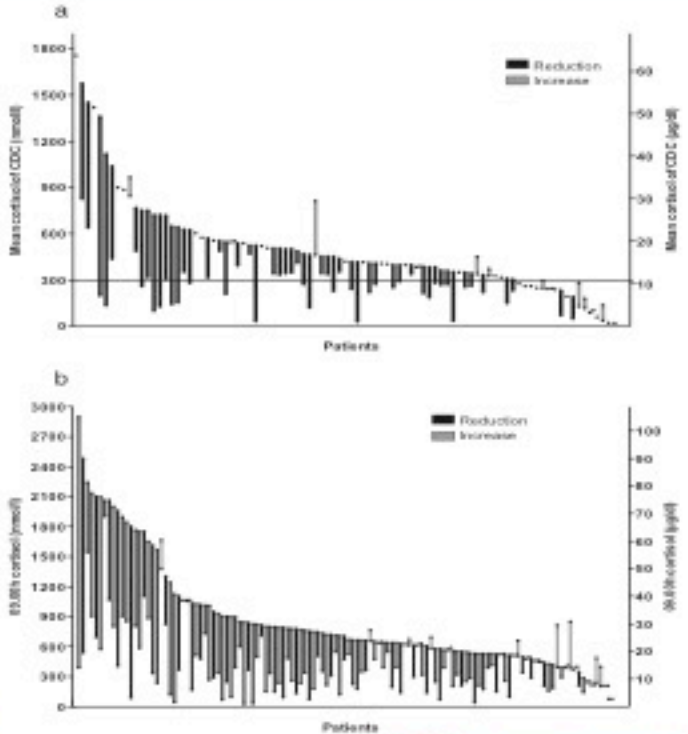
Metyrapone

ORIGINAL ARTICLE

Effectiveness of metyrapone in treating Cushing's Syndrome: a retrospective multicenter study in 195 patients

Eleni Daniel[1], Simon Aylwin[2], Omar Mustafa[3], Steve Ball[3,4], Atif Munir[4], Kristien Boelaert[5], Vasileios Chortis[5], Daniel J Cuthbertson[6], Christina Daousi[6], Surya P Rajeev[6], Julian Davis[7], Kelly Cheer[8], William Drake[9], Kirun Gunganah[5], Ashley Grossman[10], Mark Gurnell[11], Andrew S Powlson[11], Niki Karavitaki[10,5], Isabel Huguet[10], Tara Kearney[12], Kumar Mohit[12], Karim Meeran[13], Neil Hill[14], Aled Rees[14], Andrew J Lansdown[14], Peter J Trainer[15], Anna-Elisabeth H Minder[15], John Newell-Price[1]

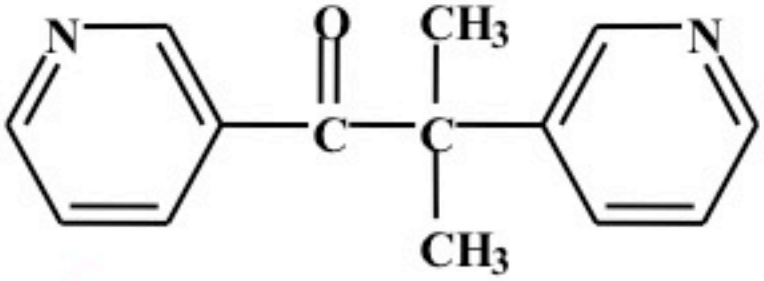
JCEM '15



- Improvement in cortisol level > 80% patients
- Cortisol control > 50% patients

Conclusions: Metyrapone is effective therapy for short- and long-term control of hypercortisolemia in Cushing's syndrome.

Metyrapone



Indications (when):

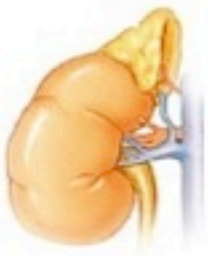
- ❑ treatment of endogenous hypercortisolism
- ❑ ACTH deficiency test
- ❑ ACTH-dependent Cushing differential diagnosis test

Pharmaceutical form (how): soft capsules 250 mg

Metyrapone: from experience to clinical practice

- **Start treatment:** variable from 250 to 1000 mg daily depending on the severity of the clinical picture
- **Posology adjustment:** within 1-4 weeks dosing cortisolemia or UFC
- **Efficacy:** normalization cortisolemia in 50-75% of treated patients
  long-term effects demonstrated for up to 6 years from the beginning of treatment
- **Replacement steroid therapy:** starts when cortisol level is normal

Metyrapone: from experience to clinical practice



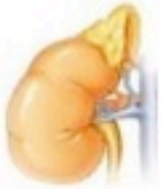
✧ Biotransformation:

- metirapol active metabolite
- inhibition 11 β-hydroxylase within 2-4 h from taking
- inhibition CYP3A4

✧ Precautions:

- High blood pressure induced by DOC accumulation

Metyrapone: safety profile



- Extensive experience: > 2800 treated patients
  follow up > 50 years

- Studies in children, elderly, pregnant or in breastfeeding women

- Side effects: consider ipokalemia and hypocortisolism
  no risk of epatotoxicity as other steroidogenesis inhibitors

Drug potentially used in Cushing's treatment

		Cushing patients	Irsutism female	Liver damage	Severe CD/CS	Pregnancy	Pediatrics
PRE-SURGERY	EAS	■			■		
	CD	■			■		
	CS	■			■		
POST-SURGERY	EAS	■			■		
	CD				■		
	CS	■			■		
MEDICAL TERAPY ONLY*	EAS	■			■		
	CD				■		
	CS	■			■		

■ Keto/Mety

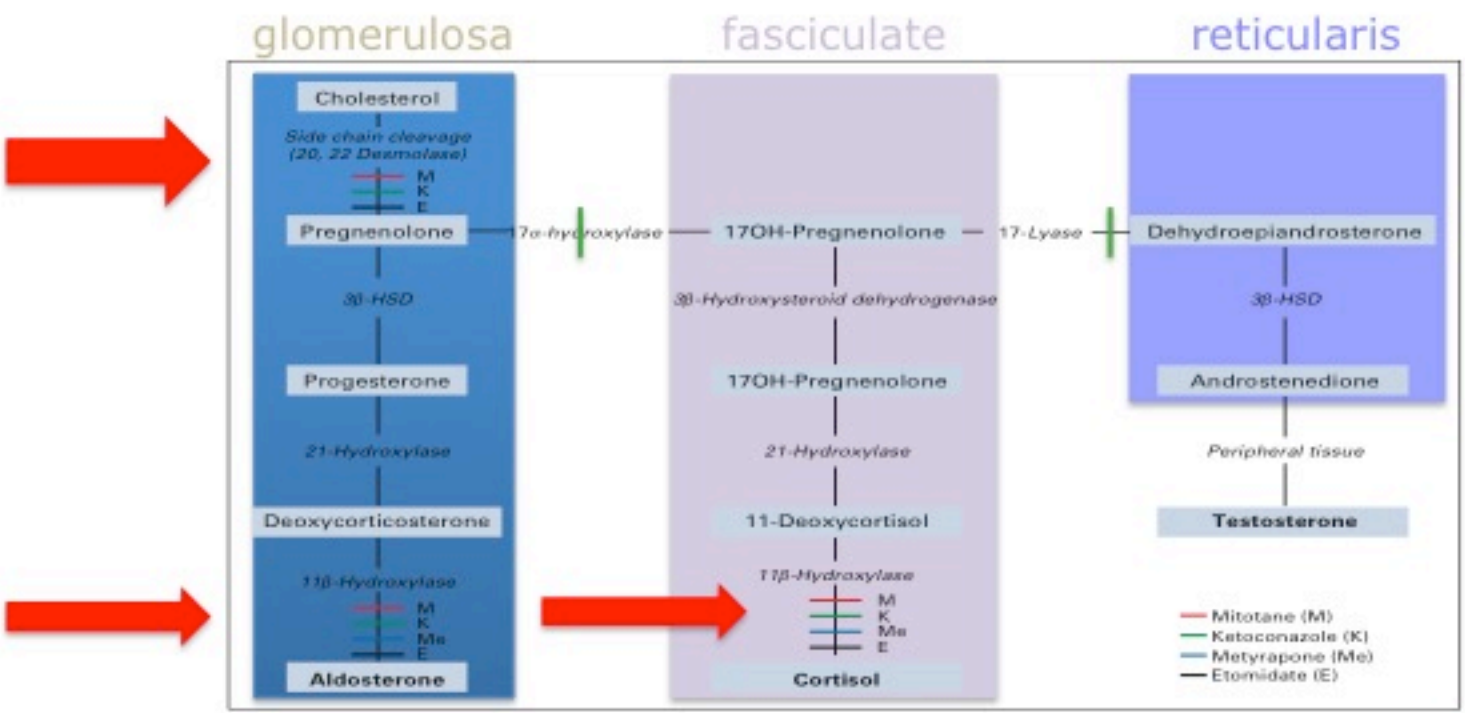
■ Pasireotide

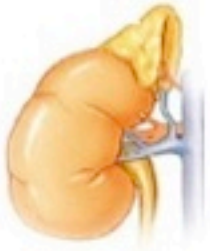
■ Keto conazole

■ Metyrapone

* In case of refuse or no other therapeutic possibilities

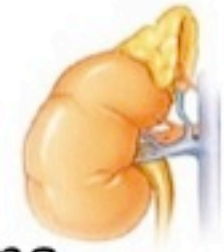
Mitotane

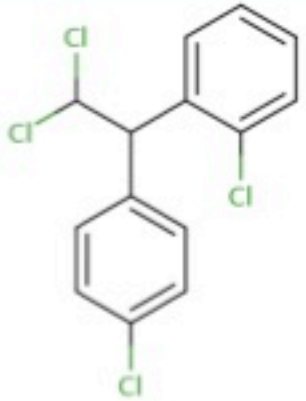




Veytsman I mod, JCO '09

Mitotane



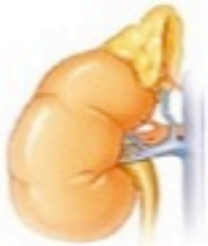


Indications (when):

- ❑ treatment of adrenocortical carcinoma
- ❑ adjunctive therapy in CD after unsuccessful TSS awaiting the effects of RT or when surgery is not feasible

Pharmaceutical form (how): tablets 500 mg

Etomidate



Indications (when):

- In emergency setting for patients who are not immediate surgical candidates and who cannot take oral medications

Pharmaceutical form (how): iv infusion (management in Intensive Care Unit)

Mifepristone

Indications (when):

- Control of diabetes or glucose intolerance secondary to hypercortisolism in patients with unsuccessful or not surgical candidate

Pharmaceutical form (how): tablets 300 mg per day

Mifepristone

- Pharmacology: glucocorticoid receptor antagonist and antiprogestin

- Posology adjustment: on the basis of clinical parameters such as glucose control, blood pressure, weight, depression (ACTH and cortisol sometimes elevated)

	Mechanism of action	Efficacy (%)	Common side effects
Ketoconazole	Inhibitor of CYP17A1, CYP11A1, and CYP11B1	53–88	Liver enzyme increase Gastrointestinal AEs Interactions with multiple drugs Not approved for use during pregnancy
Metyrapone	Inhibitor of CYP11B1, CYP11B2, and CYP17A1	75	Hypokalemia Hypertension Gastrointestinal AEs Hirsutism Not approved for use during pregnancy
Etomidate	Inhibitor of CYP11B1, CYP17A1, and CYP11A1	NR	Hypnosis Not approved for use during pregnancy
Mitotane	Inhibitor of CYP11A1, CYP11B1, and CYP11B2	~ 70	Gastrointestinal AEs Neurological side effects Teratogen (not approved for use during pregnancy)
Osilodrostat (LCI699)	Inhibitor of CYP11B2 and CYP11B1 at higher doses	78–92	Nausea Hirsutism Fatigue Headache Hypokalemia Not approved for use during pregnancy
Levoketoconazole (COR-003)	Inhibitor of CYP17A1, CYP11A1, CYP11B1, and CYP21A2	NR	Headache[a] Nausea[a] Mild liver enzyme increase[a] Not approved for use during pregnancy

CYP, cytochrome P450; AE, adverse event; NR, not reported. All of these drugs can induce adrenal insufficiency

[a] In patients with diabetes mellitus

Fleseriu M & Castinetti F, Pituitary '16

Drug in Cushing: developmental status

	Site of action	Drug	Mechanism of action	Development status
Adrenal-directed therapy	Steroidogenesis	Ketoconazole	↓CYP17, ↓CYP11β	Clinical practice
		Levoketoconazole		Phase III
		Metyrapone	↓CYP11β	Off-label
		Aminoglutetimide	↓CYP11A1	Stopped
		Trilostane	↓CYP3B2	Stopped
		Etomidate	↓CYP11β	Off-label
		Mitotane	↓CYP11A1, ↓CYP11β	Off-label
		LCI699	↓CYP11β	Phase III
		ATR-101	↓ACAT 1	Preclinical
	Melanocortin-2 receptor	GPS1573, GPS1574	Block to the MC2R activated by ACTH	Preclinical
Cushing adenoma-directed therapy	Somatostatin receptor	Pasireotide	Stimulate SSTRs, with more affinity for SSTR5 (pasireotide) and 2,4, and 5 (DG-3173)	Clinical practice
		DG-3173		Phase I
	Dopamine receptor	Cabergoline	Stimulates D2 receptor	Off-label
	Somatostatin and dopamine receptor	BIM23A760	Stimulates SSTRs and D2 receptor	Stopped
	PPAR-γ agonists	Rosiglitazone	Inhibits the mRNA expression of POMC	Stopped
	Retinoic acid receptor	All-*trans* RA 9-*cis* RA 13-*cis* RA	Inhibit cell proliferation and secretion	Phase II
	EGFR	Gefitinib	Regulates POMC expression	Preclinical
	Cicline-dependent kinases	R-roscovitine	Effects on cell cycle, and inhibits ACTH secretion by targeting cyclin E/E2F1 pathway	Phase II
	HSP90C-terminal domain	Silibinin	Restores glucocorticoid sensitivity	Preclinical
Peripheral therapy	Glucocorticoid type II receptor	Mifepristone	Antagonist of GR	Clinical practice

CYP17: cytochrome P45017A1 (17 alfa-hydroxylase); CYP11β: cytochrome P45011β (11 beta-hydroxylase); CYP11A1: cytochrome P45011A1 (side-chain cleavage of cortisol biosynthesis); CYP3β2: cytochrome P4503β2 (3-β hydroxysteroid dehydrogenase/Δ5-Δ4 isomerase); ACAT 1: acetyl-coA acetyltransferase 1; MC2 R: melanocortin-2 receptor; ACTH: adrenocorticotrophic hormone; SSTR: somatostatin receptor; RA: retinoic acid; EGFR: epidermal growth factor receptor; POMC: proopiomelanocortin; HSP: heat shock protein; GR: glucocorticoid receptor.

Ciato D et al, Exp Opin Invest Drugs ' 17

Museum of modern art, DC

Combination treatments

Combination treatments

Approach to the Cushing's Disease Patient With Persistent/Recurrent Hypercortisolism After Pituitary Surgery

Xavier Bertagna and Laurence Guignat

J Clin Endocrinol Metab 2013

No single option is ideal, able to provide at the same time a high success rate and a rapid onset of action, to restore a normal pituitary adrenal axis, and to have good tolerability. Close follow-up and thorough evaluation of the cortisolic status will eventually dictate a switch in treatment options and/or combination strategies over time. The tumor status and its possible oncogenic threat, the severity of the hypercortisolism, and the patient perspectives (wish of fertility) are among the major parameters that can help a multidisciplinary approach toward the best option. (***J Clin Endocrinol Metab* 98: 1307–1318, 2013**)

Combined Targeting: the "Cushingame"

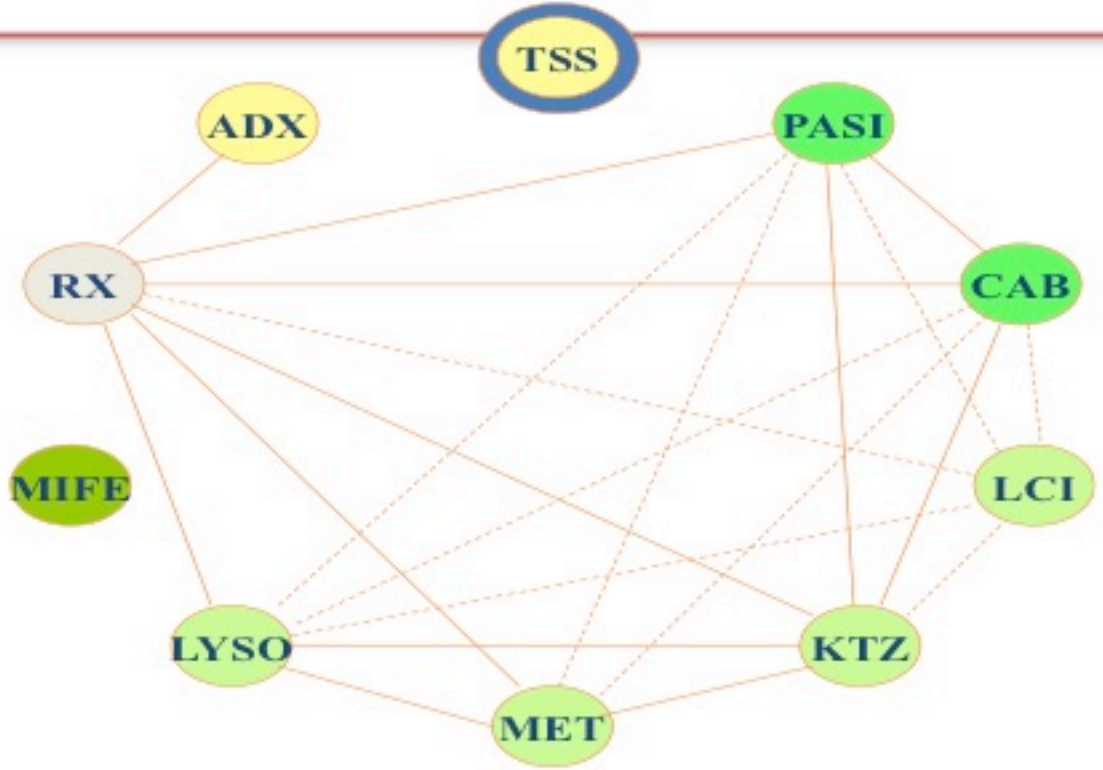


Figure 5. Combined strategies: the "Cushingame." TSS, transsphenoidal surgery; PASI, pasireotide; CAB, cabergoline; LCI, LCI699; KTZ, ketoconazole; MET, metyrapone; LYSO, Lysodren; MIFE, mifepristone; RX, radiotherapy; ADX, adrenalectomy.

Clinical studies on pasireotide + cabergoline + ketoconazole

Pasireotide Alone or with Cabergoline and Ketoconazole in Cushing's Disease

Richard A. Feelders, N ENGL J MED 362;19 NEJM.ORG MAY 13, 2010

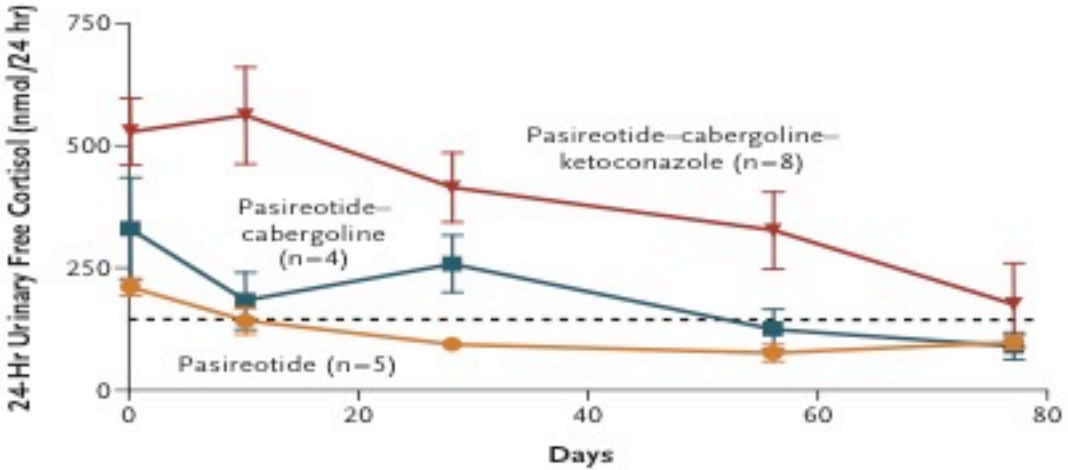
Pts started pasireotide 100 mcg *per* 3

If UFC elevated after 10 days increase pasireotide 250 mcg x 3

If UFC elevated after 28 days added cabergoline 1.5 mg day

If UFC elevated after 56 day added Ketoconazole 200 mg x 3

15/17 (88.2%) pts in remission after 80 days



Clinical studies on mitotane + metyrapone + ketoconazole

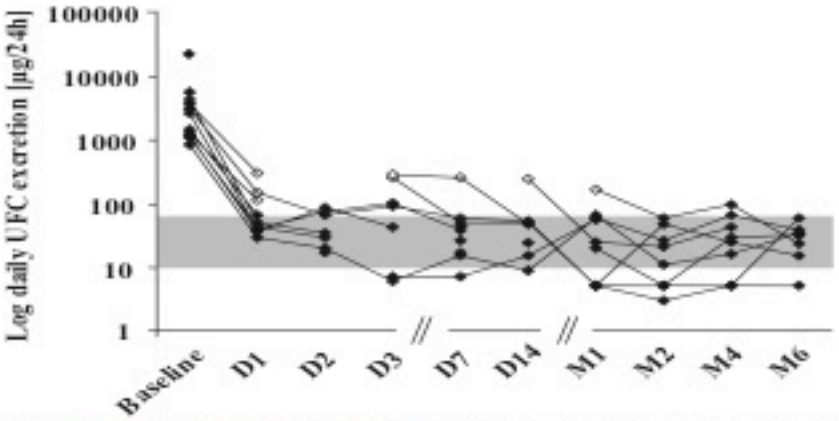
ORIGINAL ARTICLE

Endocrine Care

Mitotane, Metyrapone, and Ketoconazole Combination Therapy as an Alternative to Rescue Adrenalectomy for Severe ACTH-Dependent Cushing's Syndrome

Peter Kamenický, Céline Droumaguet, Sylvie Salenave, Anne Blanchard, Christel Jublanc, Jean-François Gautier, Sylvie Brailly-Tabard, Sophie Leboulleux, Martin Schlumberger, Eric Baudin, Philippe Chanson, and Jacques Young

(*J Clin Endocrinol Metab* 96: 2796–2804, 2011)



Conclusions: When surgical treatment for severe ACTH-dependent Cushing's syndrome is not feasible, combination therapy with mitotane, metyrapone, and ketoconazole is an effective alternative to bilateral adrenalectomy, a procedure associated with significant morbidity and permanent hypoadrenalism.

Radiant treatments

Phillips collection, DC

When and to whom radiant treatment

SPECIAL FEATURE

Clinical Practice Guideline

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, and Antoine Tabarin

J Clin Endocrinol Metab, 2015, 100(8):2807–2831

- We must confirm that medical therapy is effective in cortisol normalization before RT

When and **to whom** radiant treatment

First-line approach

✧ Mass effect or invasion by corticotroph adenoma

Second-line approach

✧ Inefficacy of TSS or recurrent CD not considered surgical candidates

Nieman LK et al

J Clin Endocrinol Metab, 2015, 100(8):2807–2831

How Radiant Treatment

Conventional RT:

✧ Fractionated photon beam RT (sessions over 5-6 weeks)

Stereotactic radiation or radiosurgery:

✧ High accuracy in reaching the target (less than 1 mm)
✧ Minimal exposure of surrounding healthy tissues
✧ Convenience (delivered in a single session)

Radiation treatment: results

Table 1 Outcome studies of patients who received radiation therapy for Cushing's disease (published in the past 12 months, 2013–2014)

First author and publication year	Journal	Technique	Number of patients	Follow up [median or mean interval in months (range)]	Tumor margin dose (Gy)	Tumor control (%)	Biochemical remission (%)
Sheehan et al. [6]	J Neurosurgery	GKS	96	48 (12–209.8)	22	98	70
Budyal et al. [7]	Pituitary	Conformal fractionated RT	20	37.5 (12–144)	45 (in 25 fractions)	95	75
Grant et al. [8]	World Neurosurgery	GKS	15	40.2 (12–96)	35	100	73
Wilson et al. [9]	Journal of Clinical Neuroscience	SRS (LINAC)	36[a]	66 (0–183.6)	20	83	5.6 or 22.2[b]
Wattson et al. [10]	International Journal of Radiation Oncology, Biology, Physics	Proton beam	74	52 (6–247.2)	20	98	54[c]

GKS Gamma knife™ radiosurgery, *LINAC* linear accelerator, *RT* radiation therapy, *SRS* stereotactic radiosurgery

[a] In addition, one patient received fractionated stereotactic radiotherapy and 13 patients received conventional radiation therapy and were included as historical controls

[b] Biochemical remission was achieved in 5.6 % of patients based on serum cortisol levels and in 22.2 % of patients based on the results of 24 h urine free cortisol

[c] Actuarial remission rate (at 36 months)

Tritos NA & Biller BMK Pituitary '15

Radiation treatment: effects

- ✧ Tumor control up to 100%
- ✧ Remission achieved in up to 75%
- ✧ Children: effective in less time (9-18 months) than adult (until 5 years)

Tritos NA & Biller BMK Pituitary '15
Acharya SV et al Pituitary '10

Radiation treatment: effects

- ✧ Withdrawal of medical therapy associated with faster endocrine remission (?)

- ✧ Diurnal rhythm is not necessarily achieved (not a valid criterion of remission)

Tritos NA & Biller BMK Pituitary '15
Acharya SV et al Pituitary '10

Radiation treatment

Risks:

- ❑ Hypopituitarism in 35-60% after 5 years
- ❑ Optic neuropathy in 1-2%
- ❑ Other cranial neuropathies 2-4%
- ❑ Secondary neoplasia (meningioma)

Loeffler JS & Shih HA JCEM '11

Thank you

DC