



## LE INNOVAZIONI NELLA TERAPIA DELLA SINDROME DI CUSHING

# LA TERAPIA COMBINATA: QUANDO E QUALE?

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# Combined therapy: when and which one?

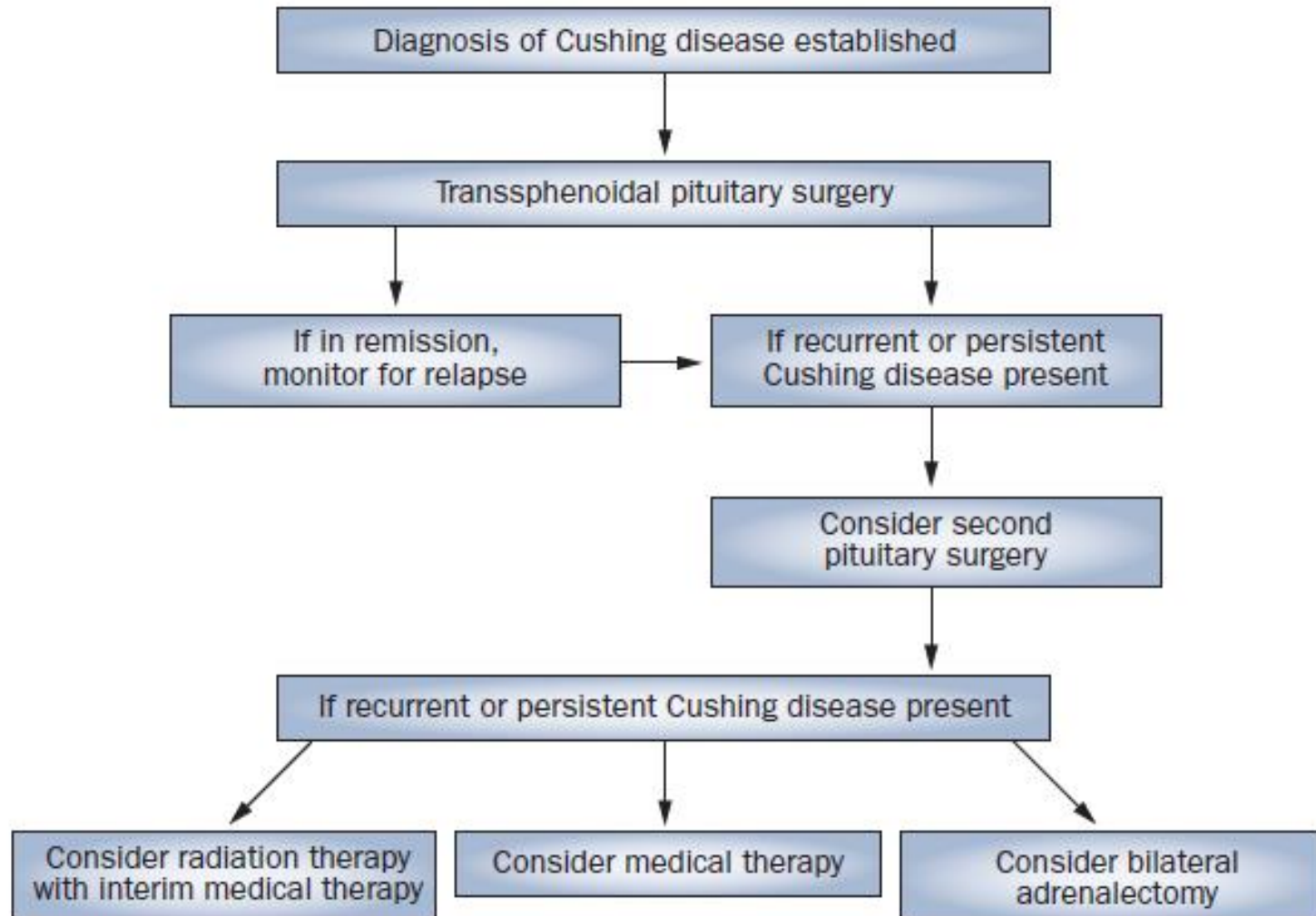


...combined therapy ?

"...Combination therapy or polytherapy is the use of more than one medication or other therapy.

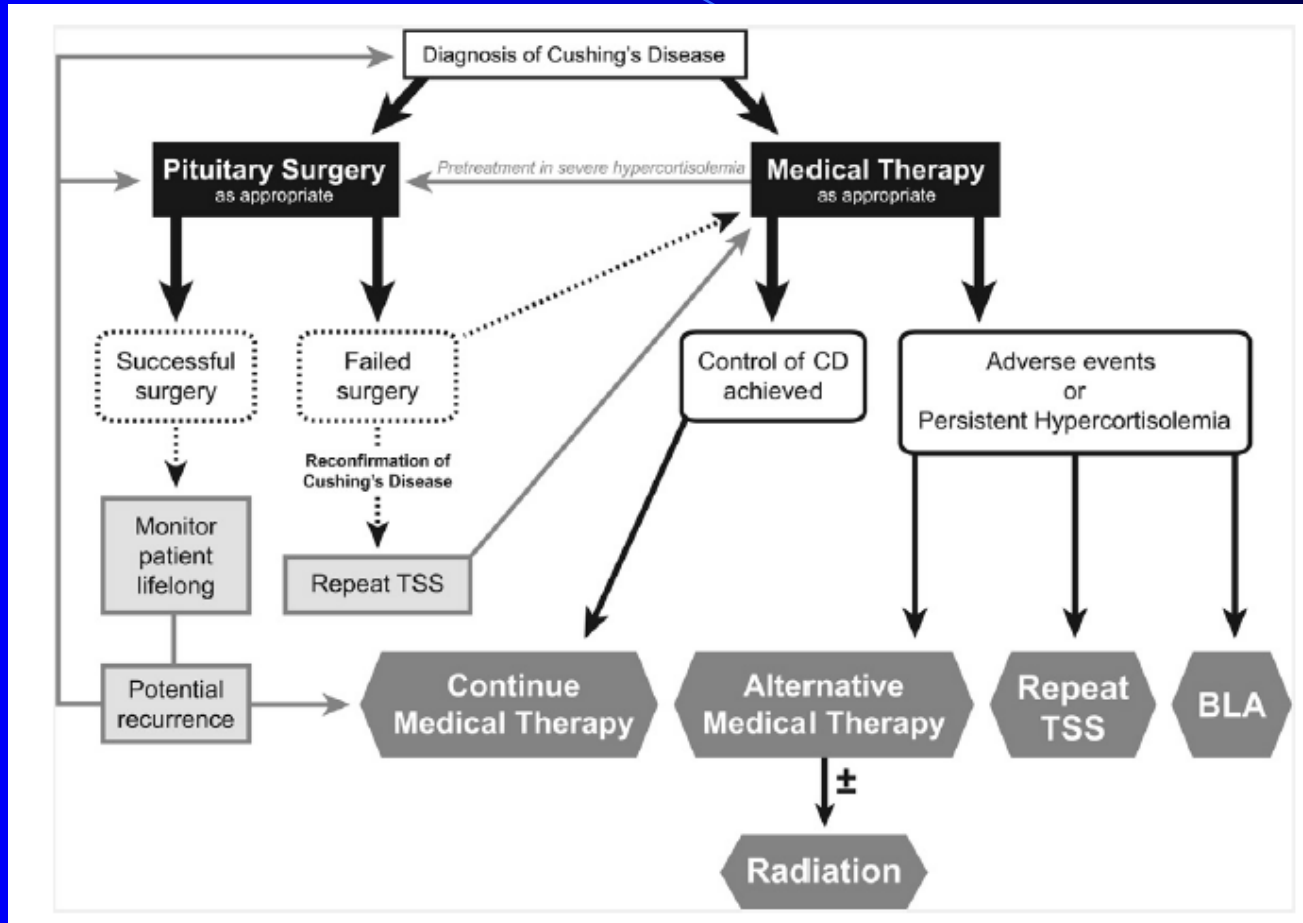
Typically, these terms refer to using multiple therapies to treat a single disease, and often all the therapies are pharmaceutical"

# Combined therapy: when and which one?



Nicholas A. Tritos, Beverly M. K. Biller and Brooke Swearingen

# Combined therapy: when and which one?



Maria Fleseriu

Neurosurg Clin N Am 23 (2012) 653–668

# Combined therapy: when and which one?

**Table 1**

**A summary of drugs, commercially available and under clinical investigation**

A	Glucocorticoid receptor blocker (act to block effects of hypercortisolemia)	Mifepristone
B	Modulate ACTH (act at the tumor level to modulate ACTH release)	Somatostatin receptor ligands: <ul style="list-style-type: none"> <li>• Pasireotide–SOM 230</li> <li>• Octreotide</li> </ul> Dopamine agonists <ul style="list-style-type: none"> <li>• Cabergoline</li> <li>• Bromocriptine</li> </ul> Other agents tried but not uniformly effective <ul style="list-style-type: none"> <li>• GABA agonists</li> <li>• Valproic acid</li> <li>• Serotonin antagonists</li> <li>• PPAR gamma</li> </ul> In vitro/animal models <ul style="list-style-type: none"> <li>• Alpha 1 adrenergic receptor antagonist</li> <li>• Retinoic acid</li> <li>• EGFR inhibitors</li> </ul>
C	Inhibitors of steroidogenesis (blockage of adrenal enzymes implicated in cortisol synthesis)	<ul style="list-style-type: none"> <li>• Ketoconazole</li> <li>• Mitotane (approved in Europe)</li> <li>• Etomidate</li> <li>• Metyrapone</li> <li>• Ketoconazole + Metyrapone + Etomidate</li> <li>• Aminoglutethimide (no longer available)</li> <li>• Trilostane (no longer available)</li> </ul> In clinical trials <ul style="list-style-type: none"> <li>• LCI (<a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>)</li> </ul>
D	Combination therapy using drugs from different groups	<ul style="list-style-type: none"> <li>• Pasireotide + Cabergoline + Ketoconazole</li> </ul>

# Combined therapy: when and which one?

## Box 1

### Clinical practice

- Ketoconazole at a dose of 200 mg two or three times daily, and check liver function and 24-hour UFC within 1 week.
- If clinical signs of adrenal insufficiency, measure morning cortisol as soon as possible, stop drug for 1 day. Start replacement glucocorticoids if needed.
- If UFC still high, increase to 400 mg twice daily.
- If not well tolerated or no effect in 2 to 3 months, switch to a different drug.
- Consider possible combination therapy.

Data from references.<sup>6,25,33,44</sup>

6. Biller, B. M. et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J. Clin. Endocrinol. Metab.* **93**, 2454–2462 (2008).
25. Bochicchio, D., Losa, M. & Buchfelder, M. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. *J. Clin. Endocrinol. Metab.* **80**,
33. Trainer, P. J. et al. Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. *Clin. Endocrinol. (Oxf.)* **38**, 73–78 (1993).
44. Valassi, E. et al. Delayed remission after transsphenoidal surgery in patients with Cushing's disease. *J. Clin. Endocrinol. Metab.* **95**, 601–610 (2010).



# Combined therapy: when and which one?

## Steroidogenesis inhibitors

Cortisol levels reduction

No effect on pituitary mass

↳ increase in ACTH secretion

↳ possible escape

↓  
**secondary failure**

# Combined therapy: when and which one?

These limitations of monotherapy can be addressed by combining ketoconazole with additional adrenal enzyme inhibitors in the following four-step sequence: first, ketoconazole 250 mg three times daily, increasing to 400 mg three times daily, if needed; second, the 11 $\beta$ -hydroxylase inhibitor metyrapone 250 mg three times daily, increasing to a total of 4 g per day if needed (while watching for increased ACTH secretion leading to increased adrenal androgen and mineralocorticoid production, leading, in turn, to hirsutism and hypertension); third, 250 mg aminoglutethimide three times daily, which inhibits cholesterol side-chain cleavage, reducing the excess androgen and mineralocorticoid production seen with ketoconazole plus metyrapone; and finally, the addition of mitotane, an inhibitor of four P450 enzymes, if a combination of ketoconazole, metyrapone, and aminoglutethimide fails to control hypercortisolemia (Figure 2).

NATURE CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM

2008 Oct;4(10):560-8

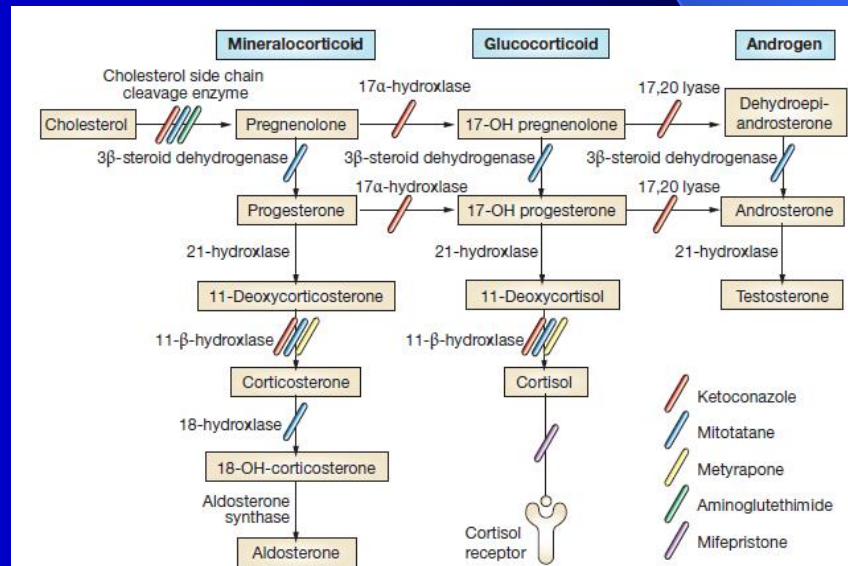
Manish K Aghi

ketoconazole 250-400 mg x 3 daily

+ metyrapone 250 mg - 4 g x 3 daily

+ aminoglutethimide 250 mg x 3 daily

+ mitotane





# Combined therapy: when and which one?

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

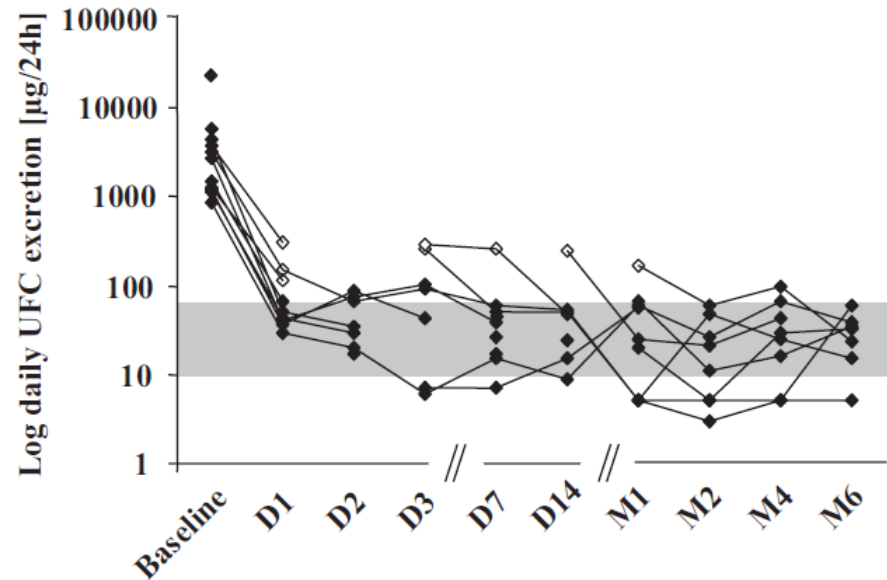
Kamenick et al. J Clin Endocrinol Metab, September 2011, 96(9):2796–2804

Prospective trial with 11 severe CD patients treated with mitotane, metyrapone and ketoconazole

Mitotane 3-5 g/day

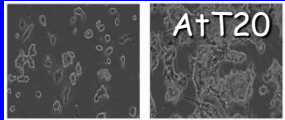
Metyrapone 3 - 4.5 g/day

Ketoconazole 400 - 1200 mg/day



marked clinical improvement and important decrease in UFC

# Combined therapy: when and which one?



Research

E GENTILIN and others

Mitotane effects on  
corticotrophs

218:3

275–285

## Mitotane reduces human and mouse ACTH-secreting pituitary cell viability and function

Erica Gentilin<sup>1,2</sup>, Federico Tagliati<sup>1</sup>, Massimo Terzolo<sup>3</sup>, Matteo Zoli<sup>4</sup>,  
 Marcello Lapparelli<sup>5</sup>, Mariella Minola<sup>1</sup>, Maria Rosaria Ambrosio<sup>1</sup>, Ettore C degli Uberti<sup>1,2</sup>  
 and Maria Chiara Zatelli<sup>1,2</sup>

*Journal of Endocrinology*  
 (2013) **218**, 275–285

Mitotane directly reduces both secretory activity and viability of pituitary ACTH-secreting mouse cells

These data indicate that mitotane could have direct pituitary effects on corticotroph cells.

# Combined therapy: when and which one?

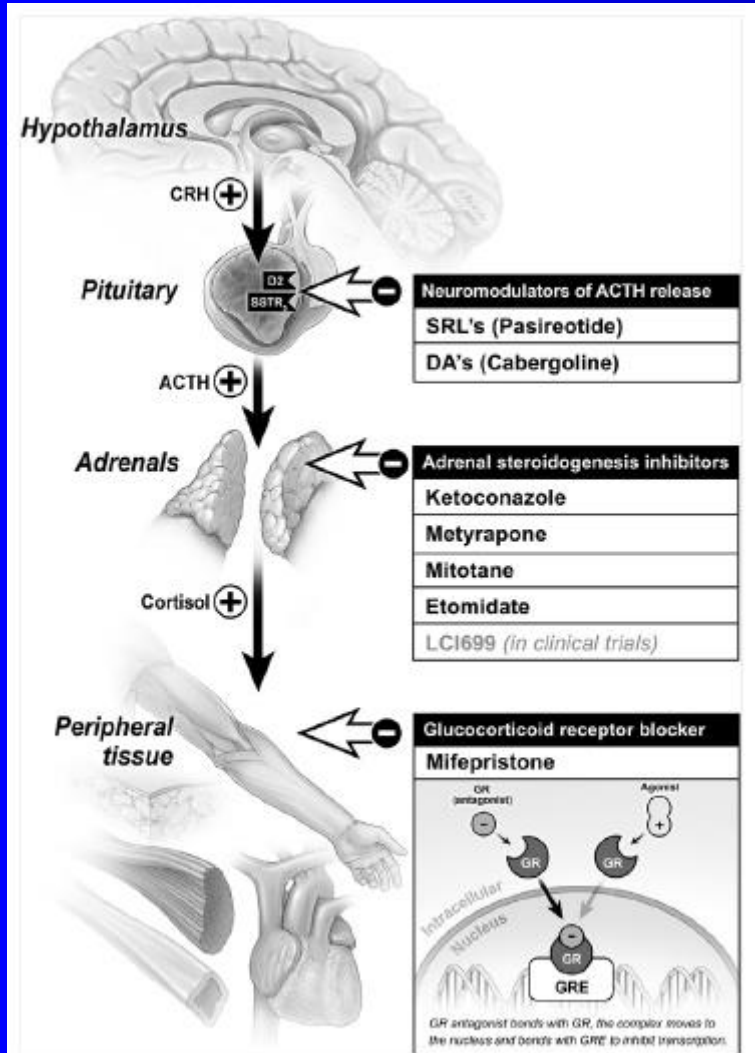
## Combining drugs

with complementary  
pharmacological  
mechanisms

higher chance of long term  
hypercortisolism control

lower drug doses

lower side effects  
incidence



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EFE 2014

# Combined therapy: when and which one?

## New developments in the medical treatment of Cushing's syndrome

R van der Pas, W W de Herder, L J Hofland and R A Feelders

"monotherapy with either cabergoline or pasireotide induces complete biochemical remission in about 25% of patients"

Prospective open-label trial (80 days)  
17 patients with CD  
treated in a stepwise manner with  
pasireotide mono or  
combination therapy with cabergoline and  
low-dose ketoconazole

Pasireotide 100  $\mu$ g x 3 daily

Day 10

Pasireotide 250  $\mu$ g x 3 daily

Day 28

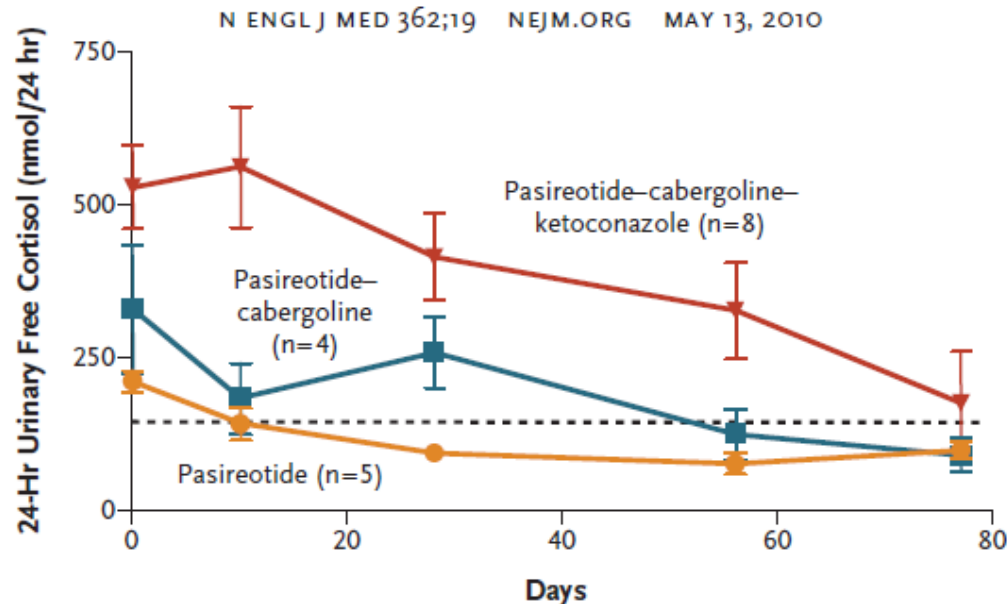
+ Cabergoline 1.5 mg every other day

Day 56

+ Ketoconazole 200 mg x 3 daily

# Combined therapy: when and which one?

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



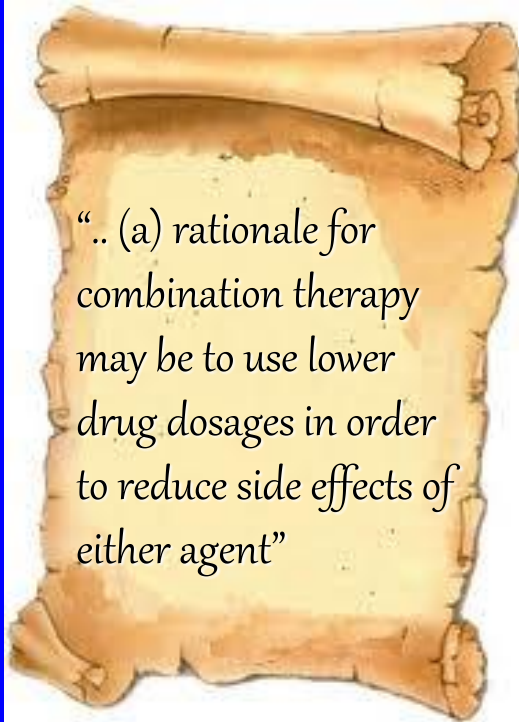
Thus, stepwise medical therapy for Cushing's disease with the use of three drugs that differentially target somatostatin-receptor subtype 5 and dopamine-receptor subtype 2 receptors in the adrenocorticotropin-secreting adenoma and steroidogenic enzymes in the adrenal cortex resulted in biochemical control in nearly 90% of patients.



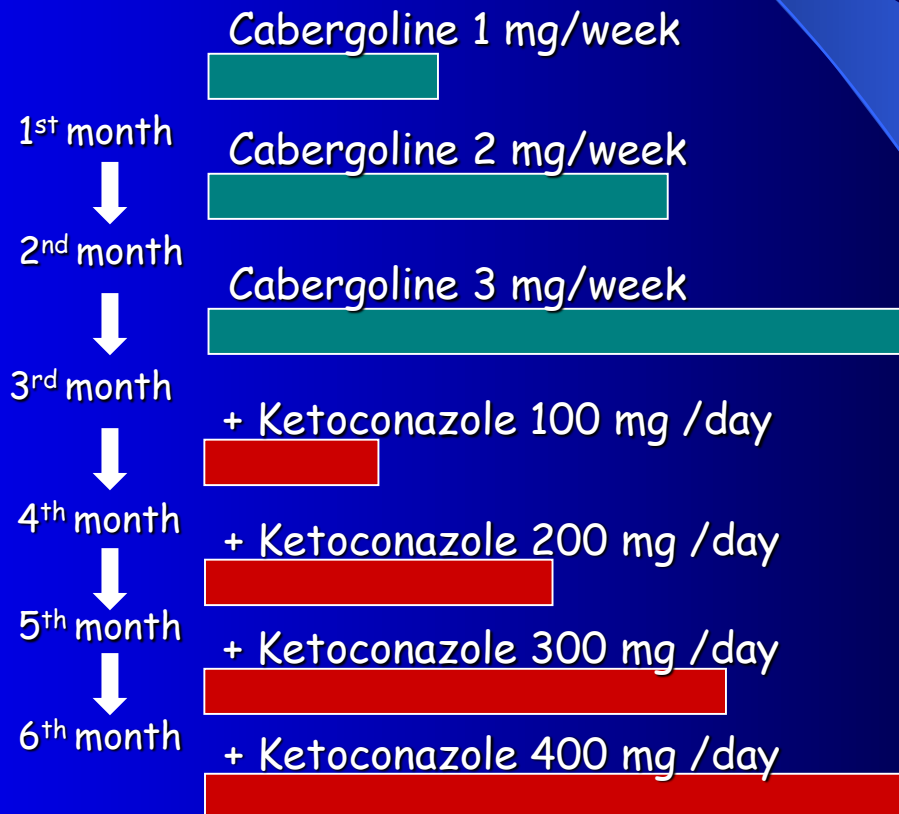
# Combined therapy: when and which one?

## New developments in the medical treatment of Cushing's syndrome

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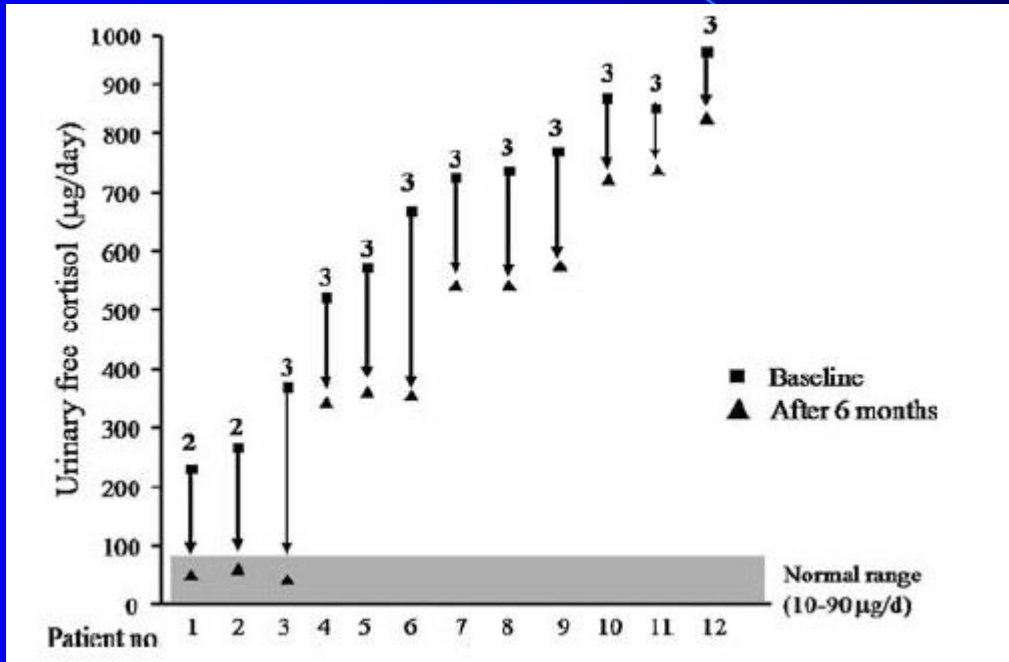


→ Prospective trial (6 months) 12 CD patients [ $CLU > 2 \times ULN$ ] treated with cabergoline mono or combination therapy with ketoconazole





# Combined therapy: when and which one?

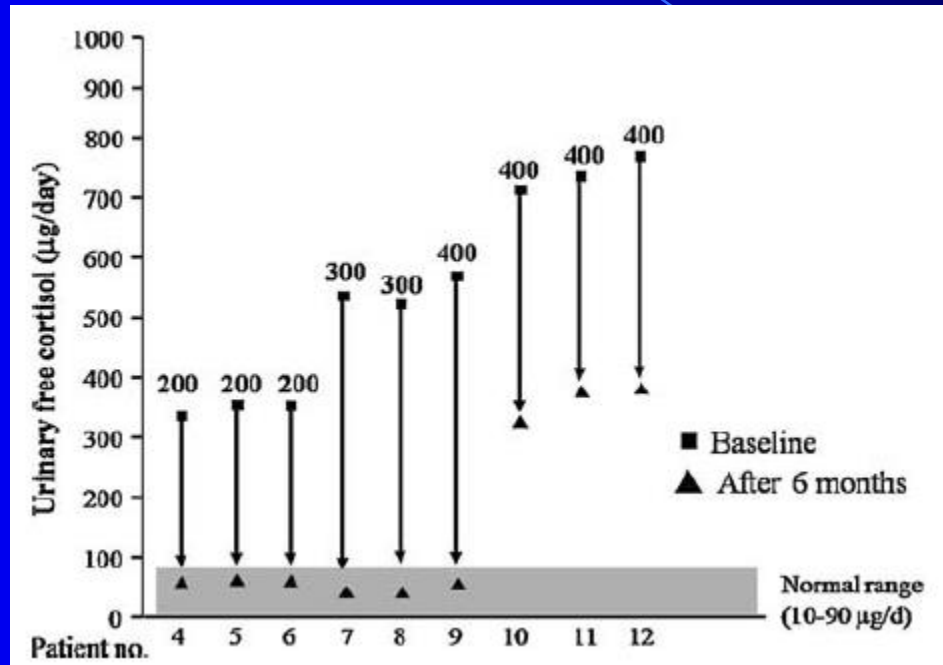


3 patients  
normalized  
UFC

Changes in 24 h UFC levels after treatment  
with cabergoline

Well tolerated

# Combined therapy: when and which one?

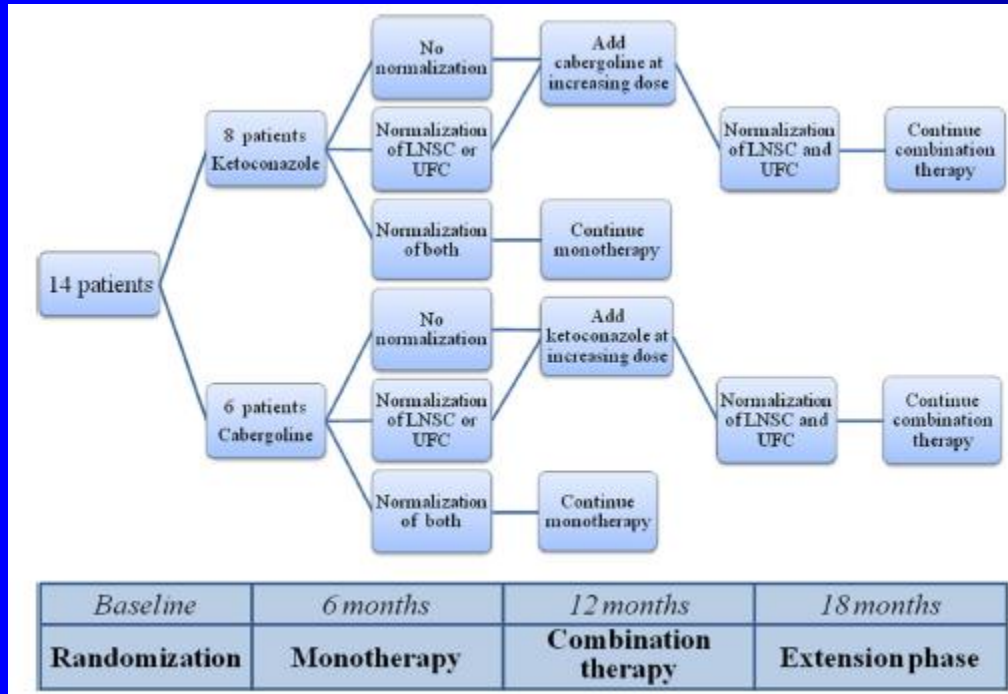


6 patients  
normalized  
UFC

Changes in 24 h UFC levels after treatment  
with cabergoline and ketoconazole

Well tolerated

# Combined therapy: when and which one?



Barbot et al.

Pituitary (2014) 17:109-117

Prospective trial (6 months) 14 CD patients [persistent/recurrent] treated with

cabergoline and then in combination with ketoconazole

ketoconazole and then in combination with cabergoline

Cabergoline 1-3 mg/week


Ketoconazole 200-600 mg /day

## NO DIFFERENCE

# Combined therapy: when and which one?

## New developments in the medical treatment of Cushing's syndrome

R van der Pas, W W de Herder, L J Hofland and R A Feelders



"combination therapy  
is indicated when  
symptomatology  
requires rapid reversal  
of cortisol excess"

→ Prospective trial with 11 severe CD patients  
treated with mitotane , metyrapone and  
ketoconazole

Mitotane 3-5 g/day



Metyrapone 3-4.5 g/day

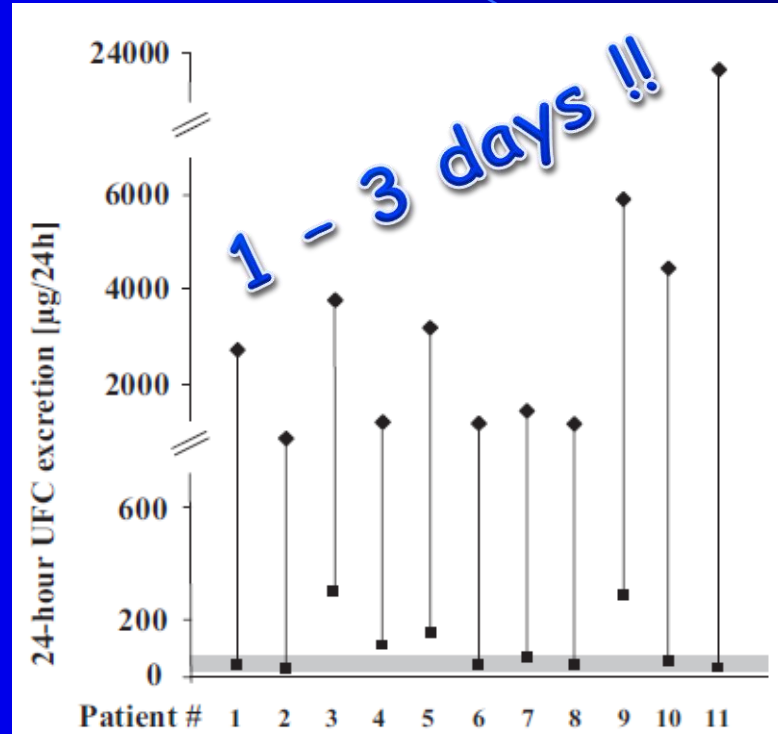


Ketoconazole 400 - 1200 mg/day



Kamenicky J Clin Endocrinol Metab, 2011, 96:2796

# Combined therapy: when and which one?



rapid decrease in UFC within 24 - 48 h

effective alternative to rescue  
bilateral adrenalectomy

# Combined therapy: when and which one?

## Predictors of response ?

degree of hypercortisolism at baseline determined the amount of drugs needed to control cortisol excess

Feelders et al. N Engl J Med 2010;362:19

patients not reaching biochemical remission had the highest UFC excretion at baseline

Vilar et al. Pituitary 2010;13:123



# Combined therapy: when and which one?

## Therapy for the complications of CD

Tatiana Mancini<sup>1</sup> Therapeutics and Clinical Risk Management 2010;6 505–516  
Teresa Porcelli<sup>2</sup>  
Andrea Giustina<sup>2</sup>

### Cardiovascular complications

"Conventional antihypertensive therapy (thiazides, ACE inhibitors, and calcium antagonists are generally considered as first choice) may be only partially effective"

### Osteoporosis

"..additional therapies, such as calcium and vitamin D supplementation and sex hormone replacement in men or women with hypogonadism, may likely be beneficial"

### Venous thromboembolic events

thromboprophylaxis

### Hypopituitarism in cured CD

# Combined therapy: when and which one?

## WARNING !

knowledge of combination  
therapy comes largely from  
case reports and  
small open-label studies



# THANKS

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