ASSOCIATION OF THE TREATMENT WITH 5 ALPHA-REDUCTASE INHIBITORS WITH THE PSYCHOLOGICAL WELL-BEING OF PATIENTS WITH BENIGN PROSTATE HYPERPLASIA

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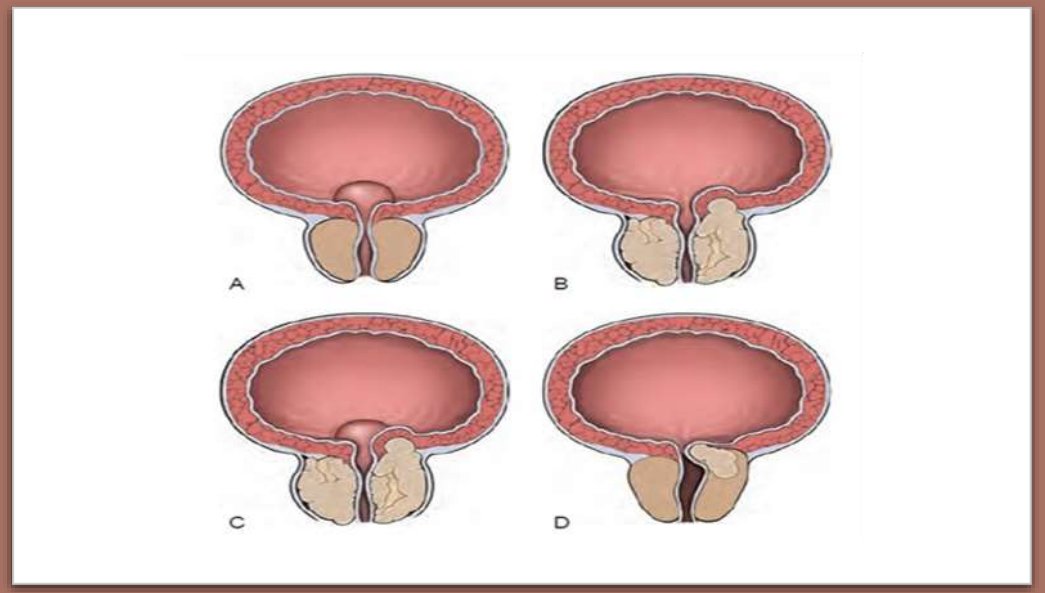
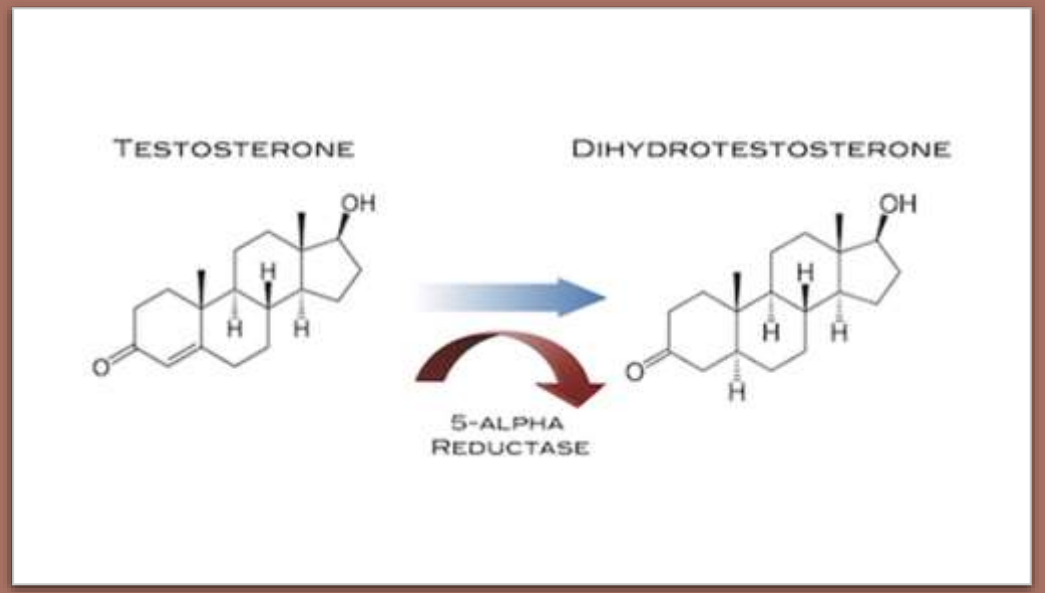
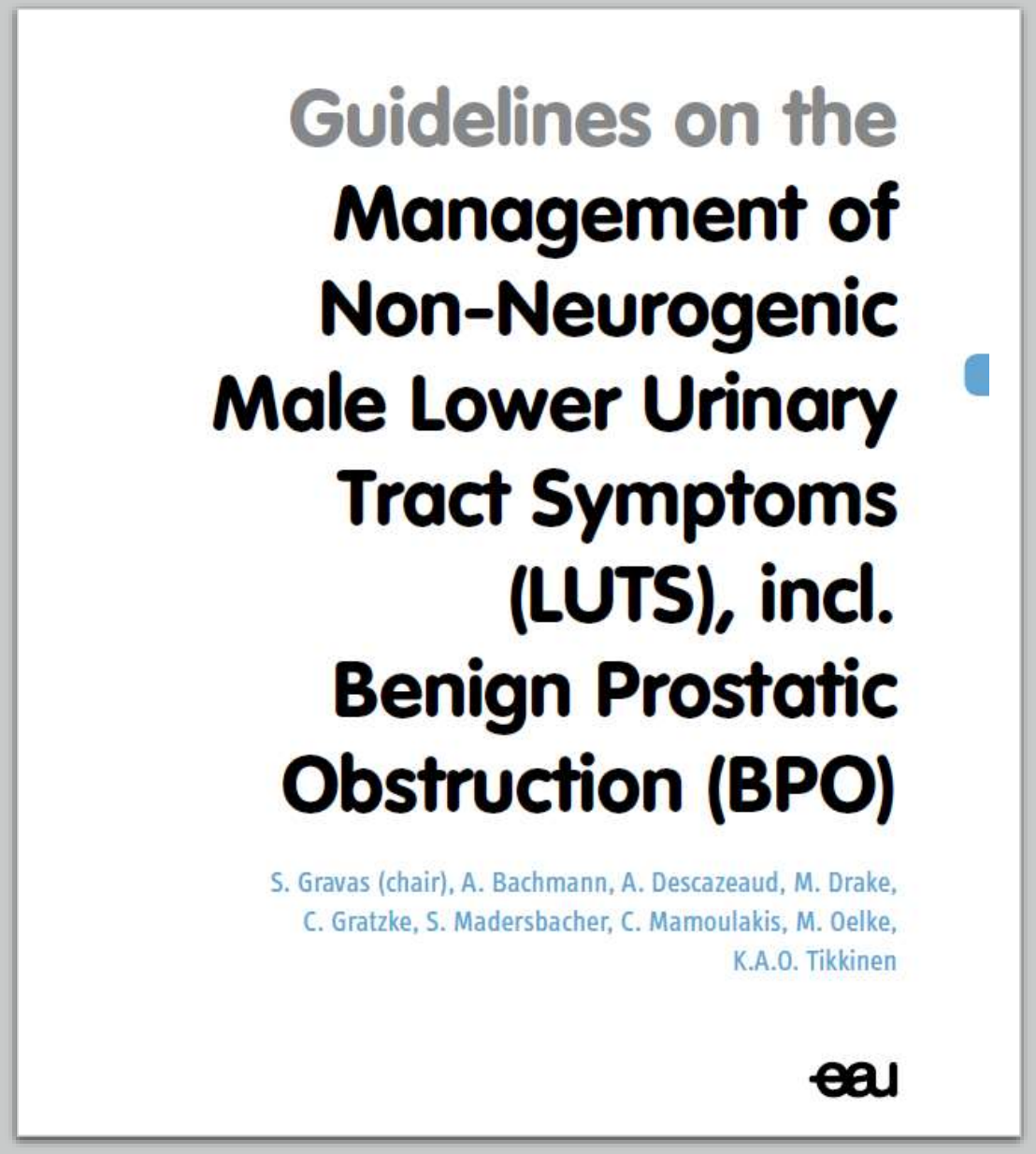
Benign Prostatic Hyperplasia BPH

- BPH = histological changes characterized by an increase in the number of epithelial and stromal cells in the transitional and periurethral zone of the prostate (fig.1).
- The primary androgen stimulator of prostate growth and BPH is dihydrotestosterone (DHT).
- DHT is produced from testosterone by 5alpha-reductase (5AR) isoenzymes type I and II (fig.2).





Berry SJ, Coffey DS, Walsh PC, Ewing LL (1984) The development of human benign prostatic hyperplasia with age. J Urol132:474–479



*https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts

Pharmacological treatment of BPH

Alpha blockers

- Moderate to severe symptoms

5 alpha reductase inhibitors (5ARI)

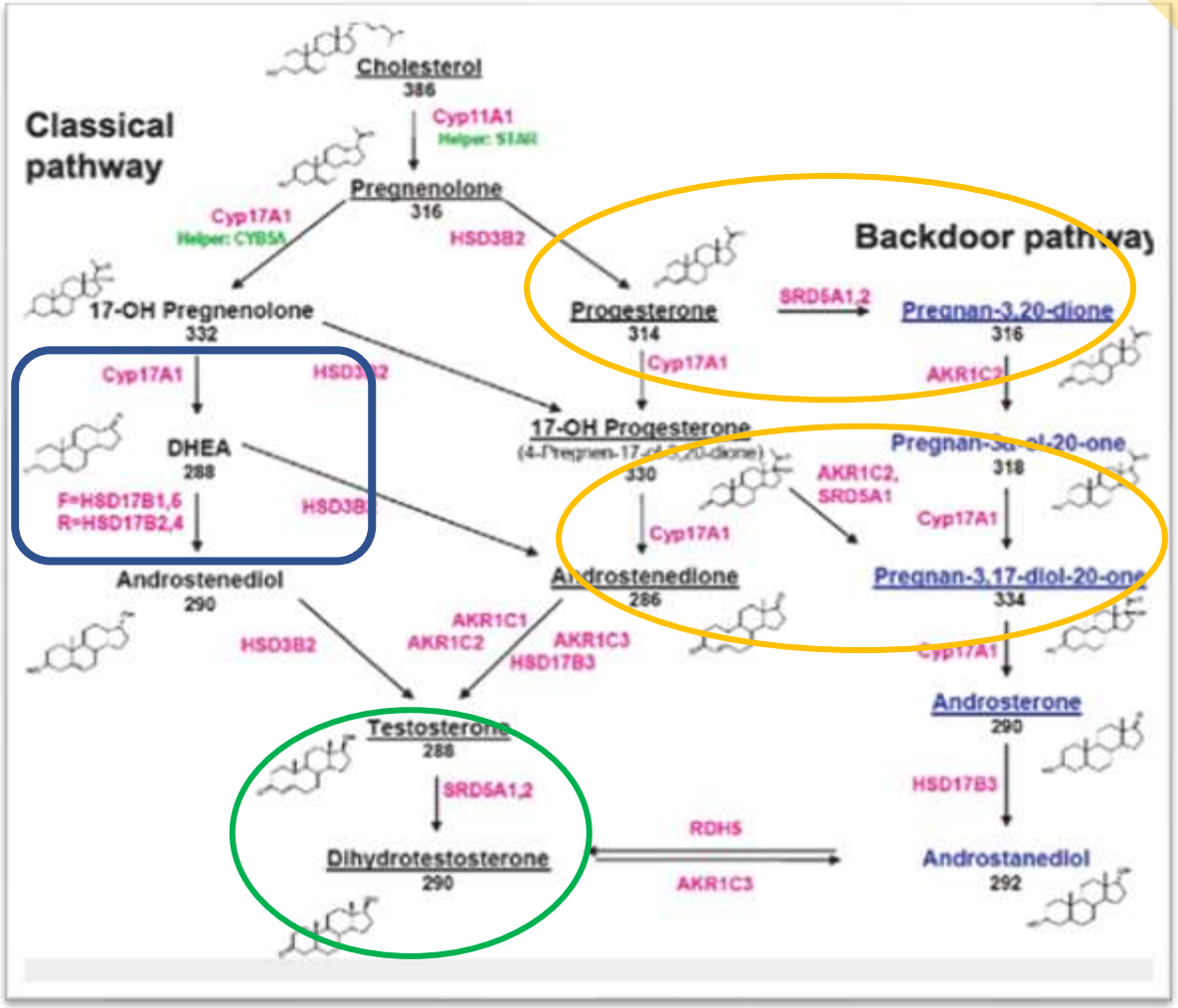
- Moderate to severe symptoms and enlarged prostate (>40mL)*

Combination therapy

- Moderate to severe symptoms and enlarged prostate (>40mL)*
- Risk of disease progression
- Not recommended for short-term treatment (< 1 year)

Steroid Bioconversion – The Role of 5 alpha reductases

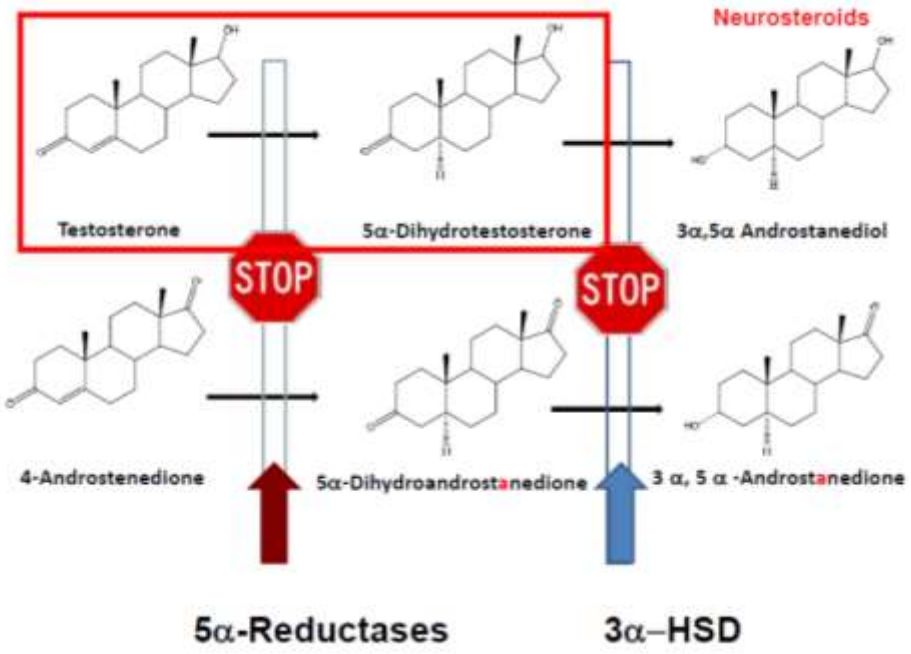
- Testosterone is transformed into dihydrotestosterone (DHT) by 5α-reductases which “feeds” the prostate (graph-1).
- 5α-reductases enable pregnanolone synthesis in the brain (antidepressant effect) (graph-2,3)
- Dehydroepiandrosterone/sulfate (DHEA/S) is the only neurosteroid that is not subject to 5α-reductase activity and acts as mood modulator (graph-4).



*Reddy D. S. (2010). Neurosteroids: endogenous role in the human brain and therapeutic potentials. *Progress in brain research*, *186*, 113–137.

Effects of 5 alpha reductase inhibitors (5ARIs)

- Inhibition of conversion of testosterone to dihydrotestosterone (no prostate “feeding”- no growth and reduction of volume).
- Five alpha-reductase activity has been identified in both neurons and glial cells in the brain and its inhibition affects neuronal function*



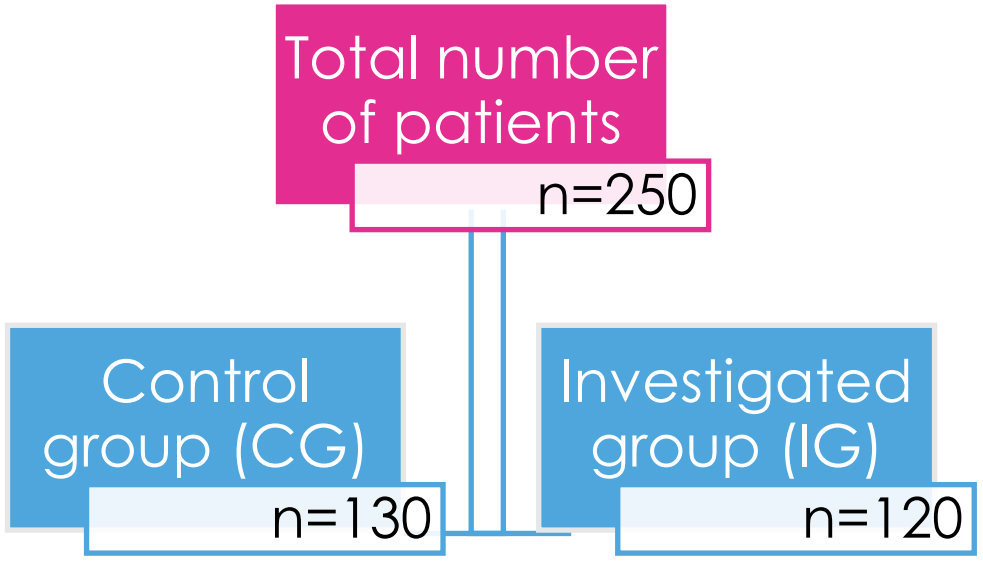
*Melcangi, R. C., Caruso, D., Abbiati, F., Giatti, S., Calabrese, D., Piazza, F., & Cavaletti, G. (2013). Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of post-finasteride patients showing persistent sexual side effects and anxious/depressive symptomatology. *The journal of sexual medicine*, *10*(10), 2598–2603.

Research

- AIM = To determine the association between DHEAS deficiency and the occurrence of side effects of 5ARI therapy that relate to the psychological well-being of patients with BPH.

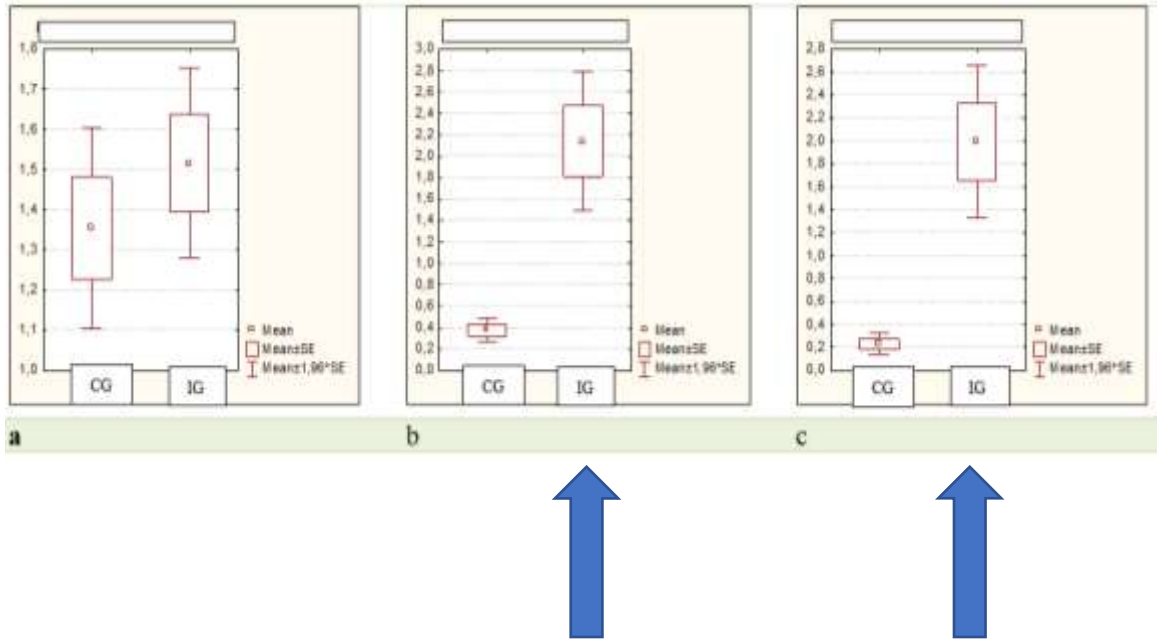
MATERIAL AND METHODS

- Quantification of BPH symptoms with the International Prostate Symptom Score (IPSS) questionnaire.
- Psychological status measured by the PhQ-9 self-evaluation questionnaire
- age 40 to 70 years
- Control group(CG) of treated with alpha blocker (n=130/250) and an investigated group (IG) treated with a combination of alpha blocker and 5ARI (n=120/250).



RESULTS of PHQ-9 questionnaire

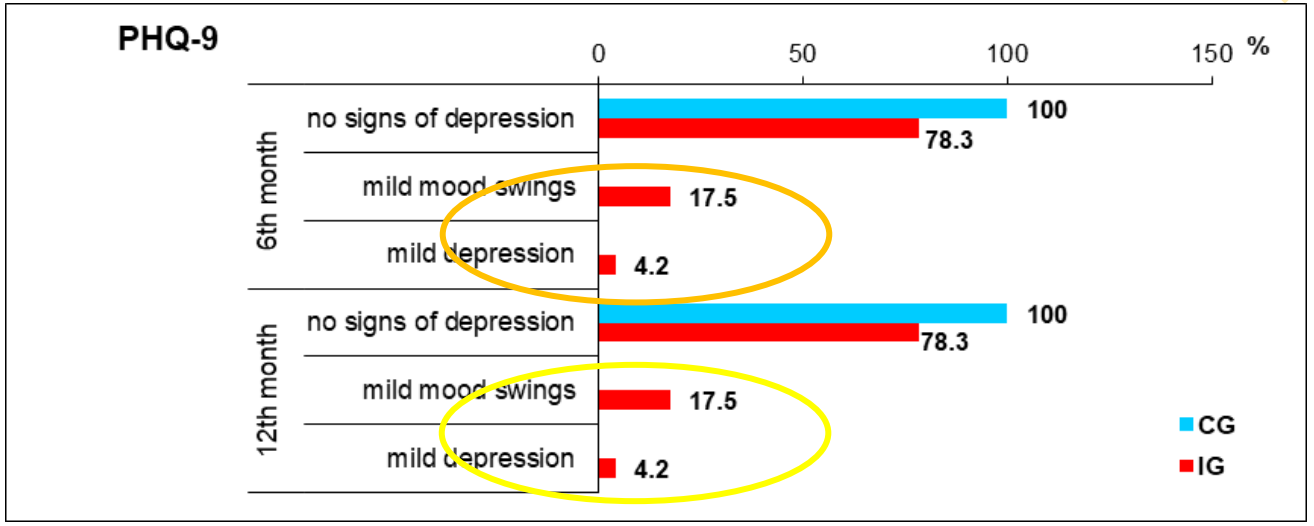
- The depression self-assessment questionnaire (PHQ-9) presented non-significantly different sums between the two groups of patients before therapy (p=0.17) (table-1)
- Significantly different sums referred after 6 months (p=0.011) (graph b) and after 12 months of therapy (p=0.046) (graph c)



Group	PHQ-9 (mean ± SD)	median (IQR)	p value
0 - month			
CG	1.35 ± 1.4	1 (0 – 3)	Z=1.38 p=0.17 ns
IG	1.52 ± 1.3	1 (0 – 2.5)	
6th month			
CG	0.38 ± 0.7	0 (0 – 1)	Z=2.52 p=0.011 sig
IG	2.14 ± 3.6	0 (0 – 1)	
12th month			
CG	0.23 ± 0.5	0	Z=1.82 p=0.046sig
IG	1.99 ± 3.7	0 (0 – 1)	

Results - correlation between the PHQ-9 scale and serum DHEAS levels

- At the beginning - NO patients with mood disorder in both groups
- 26 patients with combination therapy expressed mood disorders after 6 and 12 months of therapy (graph-1,2).
- IG = 21 (17.5%) patients with weak mood deviations, and 5 (4.2%) patients with mild depression.
- Significant correlation between the PHQ-9 scale and DHEAS ($p<0.0001$) in the IG after 6- and 12-months pharmacotherapy (table).



DHEAS & PHQ-9	CG		IG	
	Spearman R	**p-level**	**Spearman R**	**p-level**
6th month	0.016	0.86 ns	-0.573	0.000 sig
12th month	0.019	0.82 ns	-0.649	0.000 sig

DISCUSSION

Patients on combination medical therapy for BPH with lower serum DHEAS values (below 80 µg/dL) expressed varying degrees of depression.

While inhibition of 5α-reductases by 5ARIs, the biosynthesis of DHEAS in the brain remains impaired .

The inhibited steroid bioconversion on the one hand and the low serum values of DHEAS, as a direct neurosteroid, contributes to impaired psychological well-being of patients.

The use of 5-ARIs is associated with a 1.52-fold higher prevalence of depressive symptoms*

Pietrzyk, B., Olszanecka-Glinianowicz, M., Owczarek, A., Gabryelewicz, T., Almgren-Rachtan, A., Prajsner, A., & Chudek, J. (2015). Depressive symptoms in patients diagnosed with benign prostatic hyperplasia. *International urology and nephrology*, *47*(3), 431–440. https://doi.org/10.1007/s11255-015-0920-5

Rahimi-Ardabili, B., Pourandarjani, R., Habibollahi, P., & Mualeki, A. (2006). Finasteride induced depression: a prospective study. BMC clinical pharmacology, 6, 7.

CONCLUSIONS

The study proved that initially low values of DHEAS are the cause of mood disorders in patients with BPH who are on pharmacotherapy with 5ARIs.

When determining the duration of pharmacological treatment of patients with BPH, it is necessary to monitor the serum values of DHEAS.

We suggest the exogenous substitution of DHEA in patients with low serum levels (below 80 µg/dL) to maintain psychological well-being while treated with 5ARIs due to BPH.

HAPPY PATIENTS IS OUR GOAL!
THANK YOU