Journal Club at the Laboratory of Clinical Psychopharmacology of Addictions (LCPA) is a monthly gathering to discuss research papers with a focus on addiction.

Mission: to promote a better understanding of the research process and an improve ability to critically appraise research in addiction and related diseases (e.g. infectious, mental health, etc.).

Discussion topics and learning objectives include (but not limited by) the concepts of addiction, terminology used in the field, socio-cultural and biological risk factors, contemporary public health issues and policies, prevention, treatment and treatment systems.

Values:

- Learning
- Respect
- Collaboration
- Multidisciplinary
- Excellence

Please be open, flexible, realistic, and understanding!

Housekeeping notes

Video-recording

The meeting will be entirely video-recording and published on the Pavlov University website and YouTube, so if you wish not be in the recorded video, please make sure that your webcam off during the meeting.

Q&A

The seminar is interactive and we strongly encourage you to actively ask questions during the presentation but keep in mind that we have dedicated time at the end of the webinar (10 minutes) to group discussion and Q&A. Please raise your hand if you have any questions or comment. You also may use chat option to post your questions or comments. Please introduce yourself before asking questions.

Mic and Video

Please keep your mic mute during entire meeting unless you want to make a question or comment. We recommend keeping your camera on during the meeting.

Post-meeting survey

After the meeting we would like to send you the survey. Please make sure that we have your email.

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Treatment of Alcoholic Patients Using Anticonvulsant Urea Derivative Influences the Metabolism of Neuro-active Steroid Hormones - The System of Stress Markers

Shushpanova T.V. et al

Presenter: Marina D. Irkhina,
5-year medical student.

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FEATURED ARTICLE

Journal of Addiction Research & Therapy

Shushpanova et al., J Addict Res Ther 2016, 7:2
http://dx.doi.org/10.4172/2155-6105.1000271

Research article Open Access

Treatment of Alcoholic Patients Using Anticonvulsant Urea Derivative Influences the Metabolism of Neuro-active Steroid Hormones - The System of Stress Markers

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Received date: Feb 24, 2016; **Accepted date:** Mar 16, 2016; **Published date:** Mar 23, 2016

Abstract

Objective: Disturbed homeostasis of neuroactive steroid hormones (NAS) may be a risk factor for the development of mental illness and alcohol addiction; psychopharmacological drugs that modulate the activity of NAS can cause clinical effects through their impact on the balance of hormones. We investigated the levels of NAS: cortisol, adrenocorticotropin (ACTH), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone - sulfate (DHEA-S) in the blood serum of male alcoholics and healthy volunteers at baseline and at the background anticonvulsant therapy galodif, showed a positive trend in the reduction of craving for ethanol.

Journal “Journal of Addiction Research & Therapy” March 2016
Volume 7, Number 2
Impact factor: 0.37 (2016)

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PROBLEM

1. The problem of alcohol addiction and its treatment.

2. Potential mechanism – neuroendocrine system

   What is the connection between the endocrine system and addictive disorders? Which hormones are involved and why? And why does this approach take place in the treatment of alcohol addiction?

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INTRODUCTION

Endocrine changes during alcohol withdrawal syndrome:

1. Corticotropin-releasing factor hypersecretion (Valdez, 2004, Zorrilla, 2014, Stephens, 2012)
2. Hypercortisolemia (Adinoff, 1991, Esel, 2001, Ozsoy, 2008, Heinz, 1995, Keedwell, 2001) as well as in patients with delirium (Perfiliev, 2014)
3. Lower DHEA and DHEA-S (dihydroepiadrosterone and dihydroepiadrosterone sulfate)
4. Ratio of cortisol/DHEA is elevated

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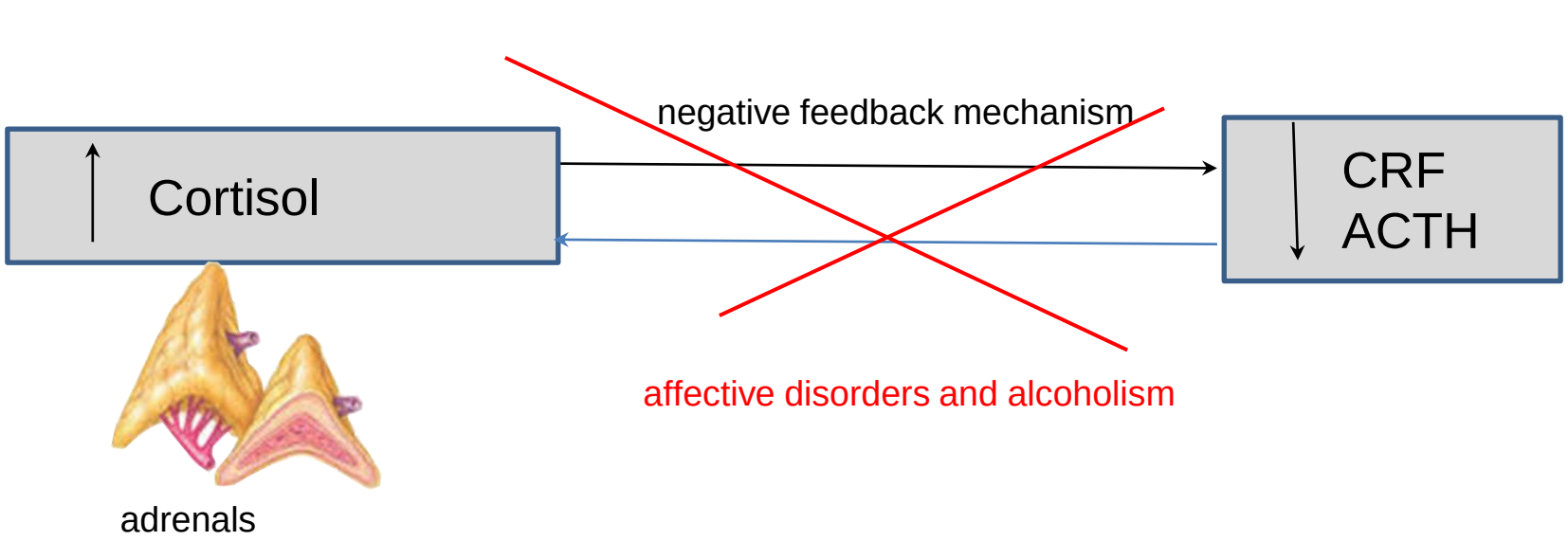
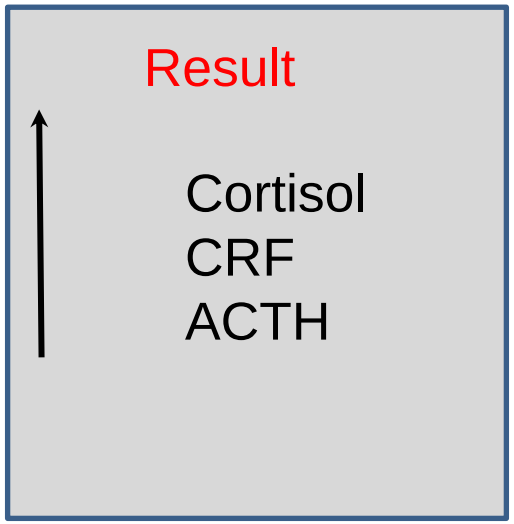
Why the levels of cortisol and ACTH elevated in patients with alcoholism, compared with of healthy people?

Among people with affective disorders (e.g. depression) and alcoholism there is a violation of a negative feedback mechanism which leads to increasing levels of Corticotropin-releasing factor, adrenocorticotropin and cortisol.





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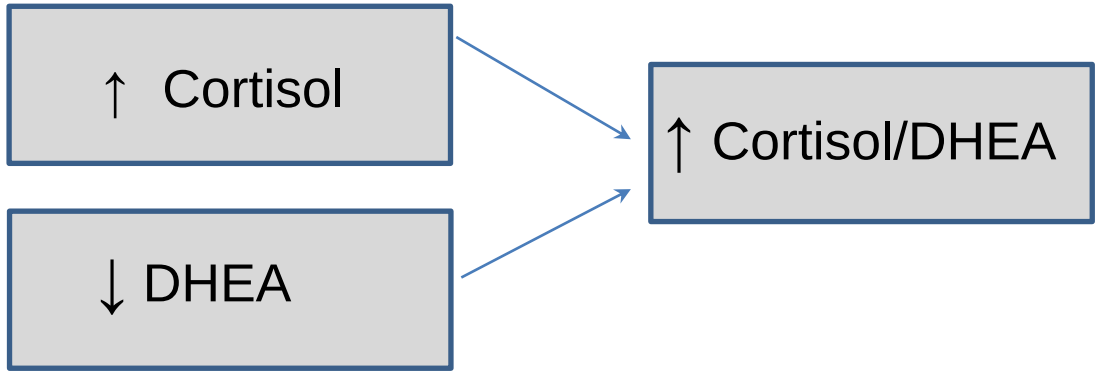
Why is DHEA and DHEA-S level reduce in people suffering from alcoholism?

Likely a result of chronic exposure to alcohol and abstinent status in these patients. DHEA has greater sensitivity to increased levels of ACTH, compared with cortisol.

Why is the ratio of cortisol/DHEA elevated in people suffering from alcoholism?

An increased ratio of cortisol/DHEA is an increased level of cortisol and a decreased level of DHAE.



STUDY OBJECTIVE

To investigate the effect of 21-day course of “Galodif” on blood steroids level among patients with alcohol withdrawal syndrome.

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WHAT IS GALODIF?

meta-chlorobenzhydrylurea (mChBGM)

Galodif is an anticonvulsant designed to treat and prevent epilepsy and alcohol use disorder.

Galodif is a non-cyclical derivative of urea (1-[(3chlorophenyl)(phenyl)methyl)

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STUDY DESIGN

An experimental comparative study of Galodif effect on neuroactive steroid hormones among patients with alcohol addiction vs. control group.

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Methods: Population

Two groups: Patient Group and Control Group

Inclusion criteria:

- Male
- For **Patient Group**: The diagnosis of "Mental and behavioural disorders due to use of alcohol, dependence syndrome» (F10.232) and "Mental and behavioural disorders due to use of alcohol, withdrawal state" (F10.302) according to ICD - 10.

Exclusion criteria:

- Patients with other comorbid psychiatric and endocrine disorders
- Reporting about using of medications that could alter the levels of steroid hormones
- Serious liver disease

Methods: Intervention

Galodif 300 mg/day (100 mg x 3 times a day) during 21 days
Same for both study group

Methods: Outcome.

Reduction of ACTH, cortisol, DHEA and DHEA-S, ratio cortisol/ DHEA in blood

Measurement:

- blood samples were collected every day in the morning on an empty stomach
- enzyme-linked immunesorbent assay (ELISA)

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Results: study flow

Enrolled, n = 91

Patient group, n = 68

Age (M ± SD) 38.3 ± 8.9 years

Control group, n = 23

Age (M ± SD) 36,50 ± 9,51 years

After 21 – day period of observation

n = 63

n = 19

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RESULTS

Type of Hormone	Volunteers		Alcoholic Patients	
	Prior to Therapy	After Treatment	Prior to Therapy	After Treatment
	(n = 23)	(n = 19)	(n = 68)	(n = 63)
ACTH (u/ml) {M ± SE}	63.82 ± 8.23	59.70 ± 9.16	82.41 ± 18.12*	66.26 ± 12.39
Cortisol (nmol/l) {M ± SE}	481.85 ± 41.31	445.30 ± 32.07	557.52 ± 2.84*	445.13 ± 7.52*
DHEA (u/ml) {M ± SE}	33.18 ± 10.54	31.92 ± 10.13	19.85 ± 5.00*	24.02 ± 6.48*
DHEA-S (ng/ml) {M ± SE}	2.48 ± 0.51	2.38 ± 0.56	1.75 ± 0.42*	1.14 ± 0.37*

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RESULTS

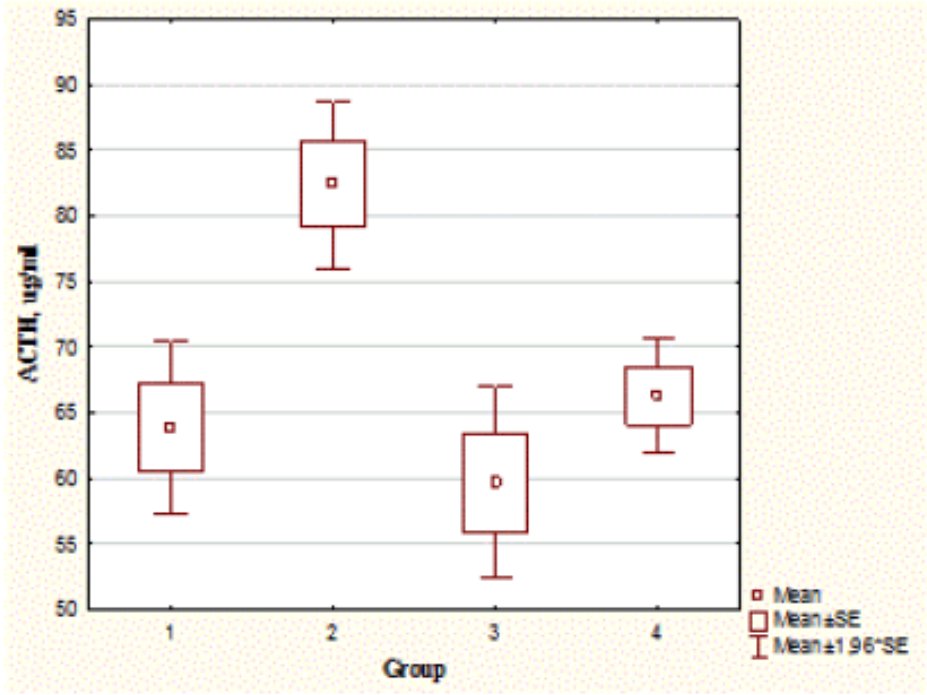

Figure 1: Statistical analysis of the level of ACTH in the blood serum of patients with alcoholism and volunteers before (Gr.1 - volunteers; Gr.2 - patients) and after treatment (Gr.3 - volunteers; Gr.4 - patients) with an anticonvulsant galodif.

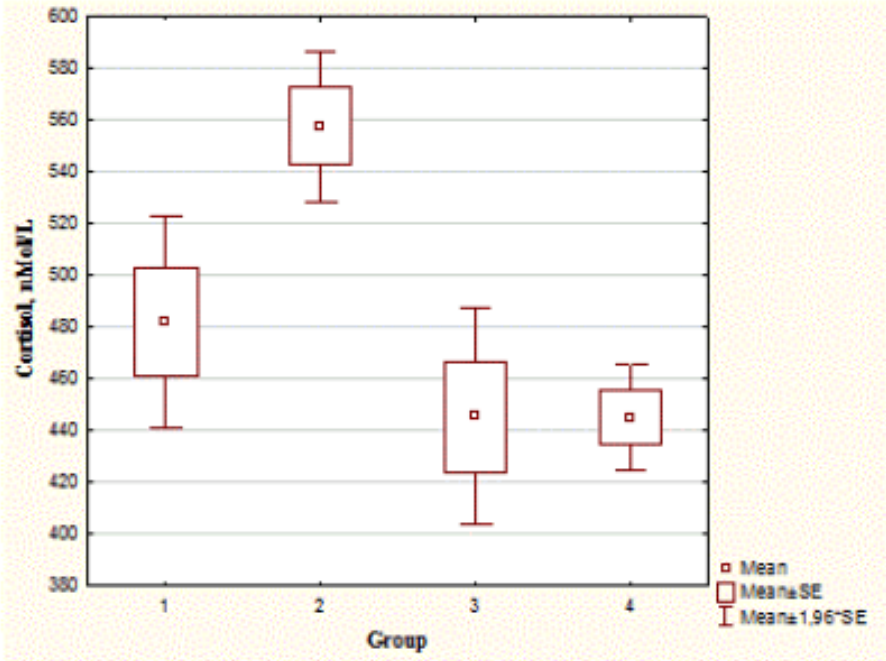

Figure 2: Statistical analysis of the level of cortisol in the blood serum of patients with alcoholism and volunteers before (Gr.1 volunteers; Gr.2 - patients) and after treatment (Gr.3 - volunteers Gr.4 - patients) with an anticonvulsant galodif.

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RESULTS

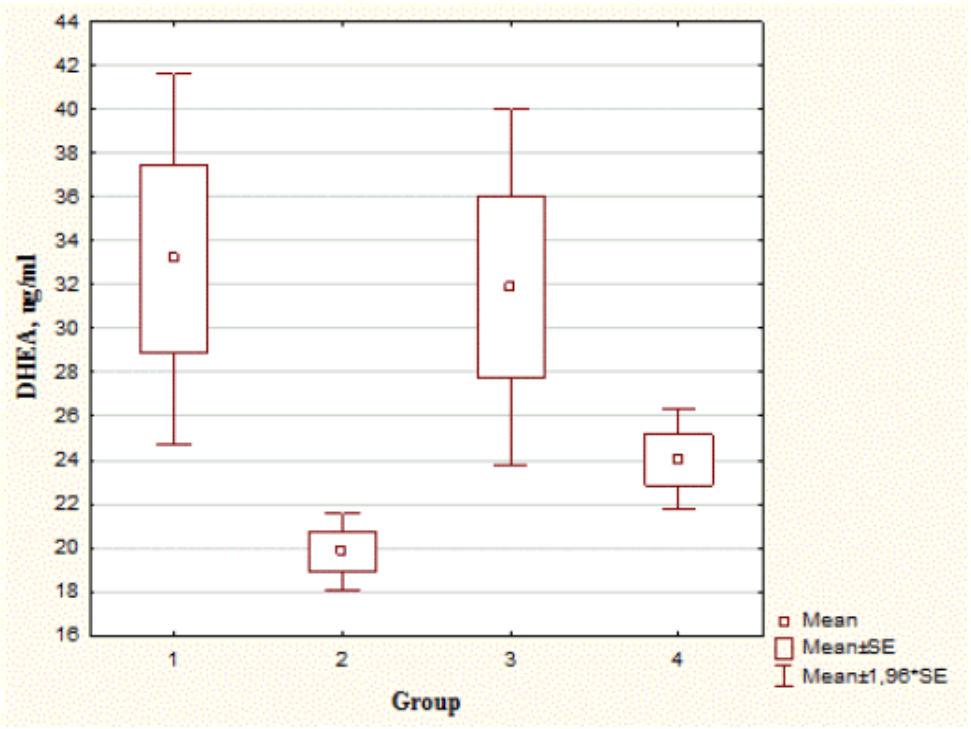

Figure 3: Statistical analysis of the levels of DHEA in blood serum in patients with alcoholism and volunteers before (Gr.1 - volunteers; Gr.2 - patients) and after treatment (Gr.3 - volunteers; Gr.4 - patients) with an anticonvulsant galodif.

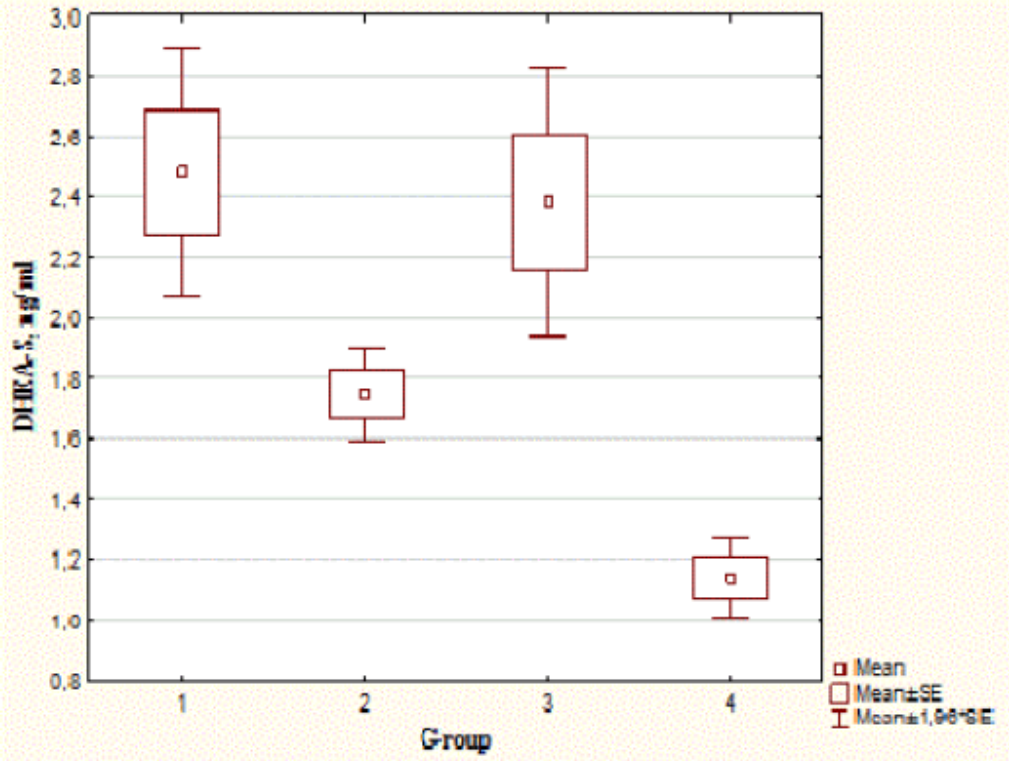

Figure 4: Statistical analysis of the levels of DHEA-S in blood serum in patients with alcoholism and volunteers before (Gr.1 - volunteers; Gr.2 - patients) and after treatment (Gr.3 - volunteers; Gr.4 - patients) with an anticonvulsant galodif.

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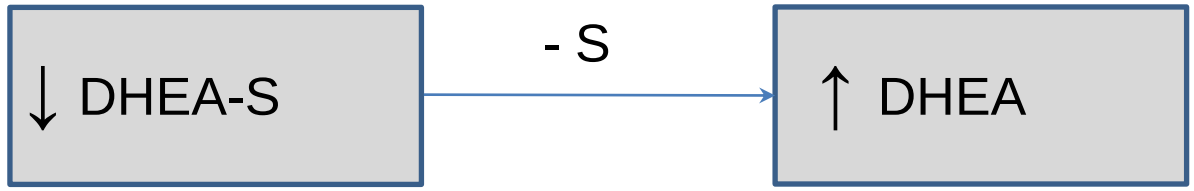
RESULTS

Why is DHEA-S level reduce in people suffering from alcoholism?

A decrease in the pool of DHEA-S in connection with its transition into the more active nonsulfated form (DHEA) having greater lipophilicity and the permeability of the blood-brain barrier.



RESULTS

Group	Cortisol/DHEA	DHEA/DHEA-S
Volunteers prior to therapy	14.52	13.38
Volunteers after treatment	13.95	13.41
Patients prior to therapy	28.07*	11.34*
Patients after treatment	18.53*	21.07*

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RESULTS

Reducing elevated levels of cortisol and the ratio of cortisol/DHEA, also associated with an increase in DHEA levels in patients with alcoholism on the background of the therapy. Is a *positive* response to treatment with an anticonvulsant galodif.

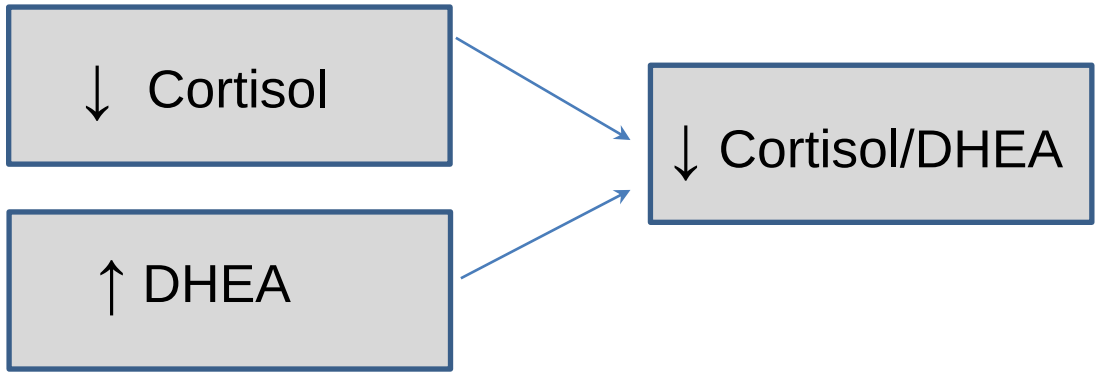

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Table 1: Levels of hormones in the blood serum of alcoholic patients and healthy volunteers before and after treatment, *: The level of significant difference $P < 0.005$.

RESULTS

A course of galodif (21 days at a dose of 300 mg/day) starting during alcohol withdrawal syndrome lead to normalization of steroid hormones balance.

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Conflict of Interest

The article did not declare a conflict of interest, however, it expressed gratitude to Mr. Vladimir N. Khudoley, who is the CEO of not only Science Technology Medicine, but also Syntegal Company since 2010. Sintegal has been producing Galodif.

Conflict of Interest

Authors declare no conflict of interest.

Acknowledgement

The authors would like to thank the anonymous reviewers for their valuable comments and suggestions on an earlier version of this paper. The authors wish to express their appreciation to Mr. Vladimir N. Khudoley, general manager of Company LLC "Science Technology Medicine" for their assistance in carrying out the work and presentations and to Scientific Program «Nauka» No.2387, Scientific Program «Nauka» No. № 4.1991. 2014/K.

DISCUSSION

1. Why did choose Galodif? Why this particular dosage? How clinically significant are the effects of Galodif? How safe is the drug and what are its side effects?
2. What are the reasons for participants from both groups to leave the study?
3. What do you think the design of this study was? Does it need to be randomized? Blinded?
4. Why did the study take hormone tests every day when only the 1st and 21st days were assessed?
5. On which clinical settings was the study conducted? An inpatient clinic or outpatient clinic? (This is important for controlling the adherence to treatment and not clear do all participants were 100% adhere to study medication or not).

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LIMITATIONS

1. Lack of details when describing inclusion and exclusion criteria.
2. Selection bias (the recruitment and enrollment processes were not described)
3. Lack of information about measurements of exclusion criteria (comorbid mental health, somatic disorders).
4. Not clear on which day of detoxication therapy the participant from Patient Group were enrolled.
5. Statistical analysis methods were not described.

Resume

To summarize, it can be noted that there were methodological difficulties (the choice of a drug, its dosage, criteria of inclusion and exclusion, etc. are not justified), but the idea of the study was interesting and requires further study of the effect of the endocrine system on addictive disorders.