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Title of the Paper:

"Antihomotoxic therapy in women with perimenopausal problems. Evaluation of therapeutic effects after Klimakt-Heel and Ignatia Homaccord preparation usage."

Introduction:

About 1/3 of women living in Poland is in menopausal age. Most of them are professionally active but for many of them it is the end of professional carrier and they need to sort out life activity priorities again (30). There emerge a lot of psychologically difficult problems in the adaptability process connected with menopause. There are changes in body image, reproduction ability is terminated, which in "normal" emotional life of women subconsciously is connected with womanhood (19, 23). Numerous ailments manifest themselves because of hormonal level decrease (19). Hence, there is continuous quest of new "treatment" methods of all disadvantageous changes connected with the perimenopausal period. Because of that the menopausal process is complex and still not known, team of specialists of different fields (gynecologist urologist internist, cardiologist endocrinologist psychiatrist, psychologist) is employed in diagnostics, treatment and prophylaxis. Lengthening life span of Polish women, gradual improvement of life level, pro-health activity "fashion", causes increase of women interest in possibilities of life quality improvement in the perimenopausal period. Large role in formation of views on possibility, or need, to care about herself in that period play mass media. Hormonal replacement therapy (HRT) is one of prophylaxis and treatment of perimenopausal period disorders elements and in some persons anti-depressive drugs usage. Different authors try to determine role which in that group of persons could play antihomotoxic therapy (5, 14, 20, 38).

Hormonal Replacement Therapy (HRT) is nowadays an important element in gynaecologist activity (25). It is well known method and used from about 60 years (28, 31). Proved beneficial effects of HRT include reduction or alleviating affective symptoms, mood changes, osteoporosis prevention and cardiovascular system diseases, colon cancer, ovaries cancer, Alzheimer disease, beneficial dermotropic effect, decrease of wrinkles, decrease of mucous membranes atrophy, atrophic changes in urogenital organs, soothing symptoms of stress urinary incontinence, inhibition of degeneration changes, decrease of general incidence of disease of aged women (31). Although benefits of this therapy are unquestioned and drugs choice is larger and larger there take place discussion according treatment schedules for obtaining the best effects (25). There are discussed precautions, risk factors and adverse effects as well (26, 31, 36). Among risk factors (relative contraindications) obesity, arterial hypertension, varices, smoking, diabetes are most often specified (26). Although most of women tolerate well HRT, in many of patients spotting, headache, body weight gain are noted (26). It is well known, that HRT usage increases risk of venous thrombosis and apoplectic strokes (8, 27, 31, 36). HRT increases risk of cholecystolithiasis and can intensify migraine symptoms also. Studies still confirm increased risk of incidence of breast cancer (9, 31). There, probably, increased risk of lupus erythematosus also exists (31). In spite of constant improvement of treatment methods and increase of HRT safety, still most of women are afraid of hormonal therapy and do not use it or interrupt it during first or second year of therapy, while time of long-term therapy is specified as 10 years or longer (31). It is estimated, that in North America and in developed countries only 20-30% women in the peri- and postmenopausal period use short term HRT, and only 5- 6% of them continue the therapy over 5 years (31). Although that fear is non adequate to risk size, therapy avoidance is the fact. Many diseases manifest themselves or intensify in perimenopausal period. One of the most of-

ten are depressive mood disorders. In women in climacteric period are found highest number of hospitalization cases because of depression (35, 37). It is commonly accepted that this advantage can be connected with higher susceptibility of women on depression during menopause period and life "richer" in physiological changes (35, 37). There is described the pathoplastic influence of involutional period on the clinical picture of depression (10). Women coming into centers dealing with menopause are, more than other, predisposed for affective disorders (29). Sex hormones role in the higher incidence of affective disorders is confirmed by fact of disease phases frequent manifestation during hormonal changes period (perinatal period, menopause, menstrual cycle), high frequency of menstrual cycle disorders during depression (32, 34). An invalidism risk in persons with depression is five times higher than in patients with other diagnosis (7, 33, 44, 44). In the study concerning medical consequences of depression carried out in US were compared data concerning 11 242 outpatients (4, 41, 43). It was found that depressive symptoms of major depression as well as not connected with it, resulted in patients functional disorders and well-being comparable with caused by frequent somatic disorders of chronic character, such as diabetes, chronic obstructive pulmonary disease (COPD), arterial hypertension and heart diseases. After 2 years of observation, about 40% of patients with major depression diagnosis had still disease symptoms and impaired social and professional functions. Persons with dystymia (1, 2, 11, 12, 13, 40) (chronic form of so called minor depression) showed up with worse prognosis - 54% of them have episode of major depression during the observation period (4, 42). In perimenopausal periods more often than in other depression are present restrictions of classical anti-depression therapy. Drug resistant depressions, atypical, chronic depression conditions, that are affections worse responding on the drugs, are frequently observed in that period (21, 32). Concurrent diseases, according to adverse effects, contraindications or interaction connected with taken drugs, exclude possibility of administration many drugs in treatment.

Towards to mentioned above phenomena and threats, and extraordinary complexity of climacterium period problems, it is very important to enable treatment possibility to persons, who of different causes do not use HRT. One of the possibilities is antihomotoxic therapy. There were not carried out studies concerning the effect of such therapy in respectively large groups of patients in Poland. There are non numerous review and scientific papers concerning the subject. There exist papers according beneficial antihomotoxic drugs effect in menopausal depression (5, 14, 20).The evaluated antihomotoxic preparations are frequently mentioned as drugs so called "second choice" in emotional and hormonal disturbances of climacterium period. Meanwhile, there exists numerous group of women in menopause requiring treatment (dramatic course of menopause, anxiety, depression and depression-anxiety disturbances), in which traditional drugs are not indicated, badly tolerated or non efficient different causes. In such cases antihomotoxic therapy could be of best significance. There is necessary to confirm good therapy effects with taking under consideration adverse effects evaluation and comparison of this therapy and the conventional therapy effects.

Aim of the study

The scientific aim of reported studies was evaluation of therapeutic effects after Klimakt-Heel and Ignatia Homaccord administration to group of women with perimenopausal problems, in which Hormonal Replacement Therapy was not used from various causes. The effects were compared with effects obtained when classical drugs were administrated (HRT and typical anti-depressive drugs). In particular were evaluated changes concerning "affective" symptoms, chosen parameters of psychical and sexual life quality and depression connected symptoms. Persons with discovered depressive disturbances during therapy were evaluated additionally in respect of therapeutic effects after Ignatia Homaccord preparation administration (in both compared groups). In the case of Klimakt-Heel preparation the long-term effect was studied, Ignatia Homaccord efficacy was evaluated according classic 6 weeks anti-depressive drugs evaluation standard. In the case of both preparations was undertaken an attempt of evaluation of adverse effects simultaneously reported by patients.

Materials and Methods:

Studied group (B) consisted of women with perimenopausal problems coming into Poradnia Menopauzy ICMP in Łódź (Menopausal Clinic), who did not start HRT because of existing contraindications or other causes (e.g. lack of patient's consent). The Klimakt-Heel preparation was administered in dose 3x1 tabl. in this group. 102 persons were included in the study.

Control group (P) consisted of women using HRT in routine way. 94 persons started the study. In this group were administered oral preparations (Estrofem, Premarin, Provera, Livial, Cyclo-Menorette, Activelle Trisequens, Femoston, Kliogest) or through-skin preparations (Estraderm TTS, Estraderm MX, Estracomb TTS) during HRT.

There was not find significant difference in age between groups. There was found significant difference in education structure. Post-secondary-school and high education was more frequent in B group. Percentage of persons of secondary school education was similar in both groups. The detailed analysis of education structure is shown in table 2. Statistically significant difference was seen in civil condition of respondents also. In control group civil status "miss" was noticed more frequently (table 3).

Table 1. Age comparison in both groups.

Age	N	Mean	Mediana	Minimum	Maximum	Standard deviation
Group B	102	51.04	51	42	64	3.608
Group P	94	51.18	51	41	63	3.196
Comparison - group P/group B			t = 1.921		p>0.05	
t-student statistics test for independent grups						

Table 2. Education in analyzed groups

Education	n	%	n	%
Elementary	7	6.86	10	10.64
Elementary professional	9	8.82	12	12.77
Secondary (not completed)	3	2.94	10	10.64
Secondary	43	42.16	39	41.49
College or university (not completed)	15	14.71	8	8.51
University	25	24.51	15	15.96
Total	102	100.00	94	100.00
Elementary:			p = 0.000017	
Elementary professional:			p = 0.000102	
Secondary (not completed) :			p = 0.017439	
Secondary :			p > 0.05	
College or university (not completed):			p = 0.041468	
University :			p = 0.000049	

Table 3. Civil status in analyzed groups

Civil status	Group B		Group P	
	n	%	n	%
Miss	4	3.92	8	8.51
Married or in free relations	78	76.47	71	75.53
Divorced or separated	12	11.76	9	9.57
Widow	8	7.84	6	6.38
Total	102	100.00	94	100.00
Miss:			p = 0.0017134	
Married:			p > 0.05	
Divorced:			p > 0.05	
Widow:			p > 0.05	

Patients with depression in B group were determined as B1 subgroup, and in P group as P1 subgroup. In these groups Ignatia Homaccord preparation in dose 3x10 drops was administered.

In B group the larger subgroup consisted of 71 patients (69.9%), who started therapy because of affective symptoms presence. 17 patients (16.7%) started therapy because of osteoporosis risk, and cardiovascular system disease prophylaxis was the aim in 14 patients (13.7%). Respectively in P group 66 (70.2%), 15 (16%), 13 (13.8%). The data were collected from reporting doctors.

There were used following study tools:

- Climacteric Index acc. Kupperman
- Quality Life Scale in Menopause
- CGI Scale - modified
- Giessen Test (GT)
- POMS Scale
- Inventory of adverse effects spontaneously reported by patient.
- Bek's Self-assessment Rating of Depression Symptoms (BSRDS)
- 17 scores Hamilton's Depression Rating Scale

Quality Life Scale in Menopause was designed in ICZMP. It evaluates intensity of biological and psychic symptoms occurring during menopause period.

GT test evaluates self-image (real or ideal), or others image. The main aim of GT test is collection of information of personality features with which the person describes itself. That is self-image or other-image, with concentration on inside or outside features (6).

POMS Scale allows comparing six mood factors (basic mood components) in studied groups.

Other study tools are so common that they do need additional comment.

CGI measurements were performed on start of therapy and after 1, 2, 3 and 6 months. The evaluation according Kupperman Index, Life Quality Scale, Beck's Questionnaire, POMS test, Giessen test were done every month for 6 months. Similarly were evaluated adverse symptoms. In the case of depressive disturbances of mood showed up in both groups, treatment with The Ignatia Homaccord preparation was included and course was monitored mentioned above scales of depression evaluation.

The depression symptoms intensity was measured on start of the therapy and after 1, 2, 4 and 6 weeks. Because that, significant part of disturbances was disclosed during the study duration, whole observation cycle was lengthen (over 6 months) for time necessary to finish studies in some respondents.

Results

97 persons from the studied group and 81 from the control group finished study. The groups did not differ significantly in age, and education structure. Initial mean level of affirmative symptoms was similar also. 2 persons from the B group dropped out of unknown reasons, 3 other continued therapy with Klimakt-Heel preparation but resigned from participation in the study. 8 persons from 13 which resigned in the P group, were excluded because of HRT adverse effects occurrence, reasons of withdrawal of 5 persons are unknown (table 4, figures 1 and 2)

Table 4. Withdrawal study participation.

Patients groups	Studied group (B)	Control group (P)
Persons included in studies	102	94
Persons that finished study	97 (95.10%)	81 (86.17%)
Persons that dropped out	5 (4.90%)	13 (13.83%)
- unknown dropout reason	2	5
- adverse effects after drugs	0	8
- lack of cooperation	3	0

The withdrawal of HRT was caused by following adverse effects: headache and dizziness – 3 persons, hypertension – 2 persons, breast pain and swelling.

Figure 1. Percentage of persons dropped out the study – B group

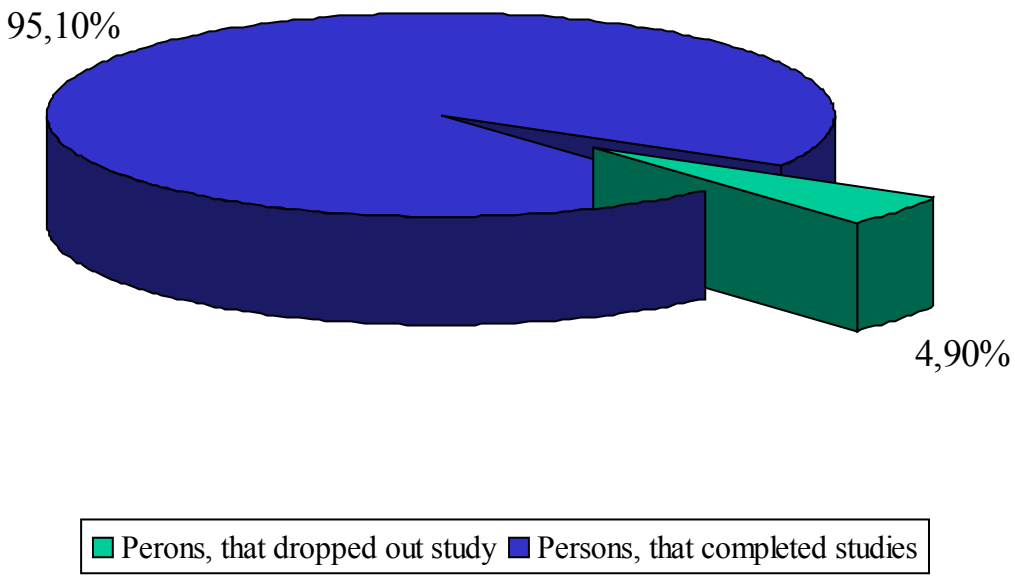
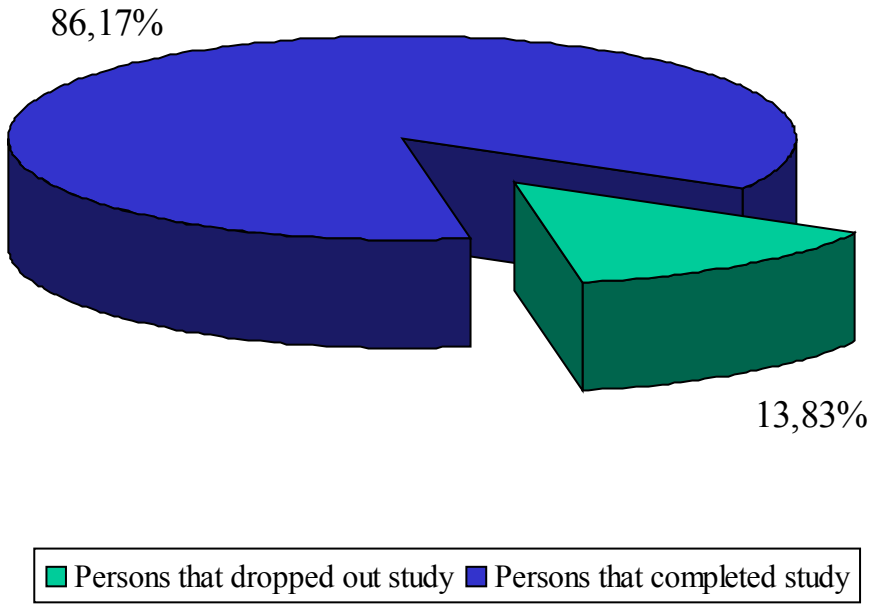


Figure 2. Percentage of persons dropped out study – P group



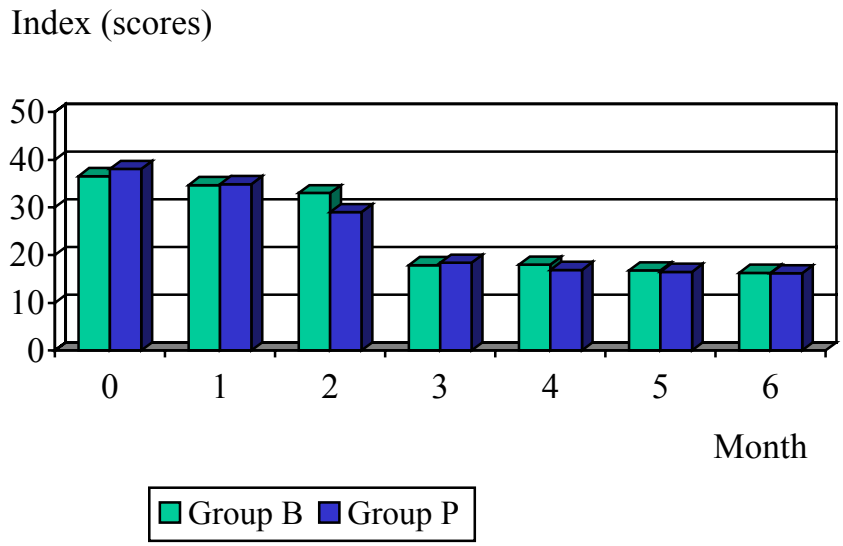
Evaluation of affective symptoms changes

In both studied groups was found the considerable improvement in scope of menopausal symptoms caused by worse ovaries activity. In the group B average reduction of Kupperman's scores was 53.8% and in the P group –51.7%. In the group B significant improvement (drop of Kupperman's Index under 20 scores) was recorded in 90 persons (88.2% of persons included in the study) and in the group P in 76 persons (80.8%). The difference is not statistically significant. Percentage of improvement estimated for persons who finished the study are respectively: B –92.8%, P – 93.8%. In this respect data of other scales were estimated on therapy start and after each full month for following 6 months. It retains attention, that measurements results from 3rd to 6th month differ slightly (statistically non significant). The detailed results are shown on figure 3 and tables 5, 6 and 7.

Table 5. Kupperman's Index changes during the study

Groups	Month of therapy						
	0	1	2	3	4	5	6
B	36.6±8.3	34.7±6.2	33±6.9	17.9±5.9	18±4.3	16.8±3.9	16.3±4.1
P	38.1±7.9	34.9±7.1	29±5.8	18.4±6.2	16.9±5.1	16.5±4.1	16.2±2.9

Figure 3. Changes in Dynamics of Kupperman's Index



There was found statistically significant difference between the start of therapy and 2, 3, 4 , 5, and 6 month of therapy ($p<0.05$). There was lack of statistically significant difference between the start of therapy and 1 month of therapy. Results of 3, 4, 5 and 6 month did not differ significantly. The mentioned relationship concerns both groups.

Table 6. Klimakt Heel – evaluation of therapeutic effects in the studied group (B).

Evaluation criterion	Evaluation in following months Number of persons (%) n=102			
	1	2	3	6
1. Kupperman's Index				
Scores reduction below 20	15(14.7%)	38(37.2%)	86(84.3%)	90(88.2%)
2. Evaluation by reporting doctor				
Very good effect	6(5.9%)	17(16.7%)	41(40.2%)	43(42.2%)
Good effect	5(4.9%)	11(10.8%)	26(25.5%)	27(26.5%)
Moderate effect	5(4.9%)	22(21.5%)	19(18.6%)	20(19.6%)
Poor effect/deterioration	86(84.3%)	52(51.0%)	16(15.7%)	12(11.7%)
3. Subjective evaluation by studied persons				
very good effect	10(9.8%)	20(19.6%)	43(42.2%)	45(44.1%)
good effect	7(6.9%)	12(11.8%)	24(23.5%)	27(26.5%)
moderate effect	9(8.8%)	19(18.6%)	21(20.6%)	20(19.6%)
poor effect/deterioration	76(74.5%)	51(50.0%)	14(13.7%)	10(9.8%)

Table 7. Klimakt Heel – evaluation of therapeutic effects in the control group(P).

Evaluation criterion	Evaluation in following months Number of persons (%) n=94			
	1	2	3	6
1. Kupperman's Index				
Scores reduction below 20	12(12.8%)	32(34.0%)	74(78.7%)	76(80.8%)
2. Evaluation by reporting doctor				
Very good effect	3(3.2%)	15(15.9%)	37(39.4%)	40(42.6%)
Good effect	4(4.2%)	12(12.8%)	23(24.5%)	22(23.4%)
Moderate effect	5(5.4%)	15(15.9%)	15(15.9%)	17(18.1%)
Poor effect/deterioration	82(87.2%)	54(57.4%)	19(20.2%)	15(15.9%)
3. Subjective evaluation by studied persons				
Very good effect	7(7.4%)	19(20.2%)	36(38.3%)	40(42.6%)
Good effect	9(9.6%)	9(9.6%)	20(21.3%)	20(21.3%)
Moderate effect	12(12.8%)	15(15.9%)	20(21.3%)	18(19.1%)
Poor effect/deterioration	66(70.2%)	51(54.3%)	18(19.1%)	16(17.0%)

Obtained results in chosen ranges of the Life Quality Scale, although describe affective symptoms as well, are shown in the next paragraph, because they concern chosen aspects of psychic and sexual life.

Results in the scope of chosen aspects of psychic and sexual life

There was noted significant improvement in psychic well-being during six month therapy with the Klimakt Heel preparation due to evaluation of patients of both analyzed groups,. In chosen subscales of Life Quality Scale were recorded significant changes in scoring according depression and anxiety symptoms and in the cognitive function. In that case, analyzed symptoms were "twice" included, that is as affective symptoms, which condition basic parameters of life quality of climacteric women. In both groups in mentioned scope (without statistic differences between groups were noted significant difference between start of therapy and its end. Changes evaluated using Beck's Self-assessment Depression Rating Scale (BSDRS) confirm drop of depression symptoms intensity both globally and in the individual subscales.

The global drop of depression symptoms in the group B measured using this scale was 31.8%, and in group P 28.6%. The difference is not statistically significant. In the POMS scale were not observed positive changes in subscales "vigor" and "confusion". Significant drop of scores was recorded in other categories (anger, tension, depression, fatigue). Similar relationships concern both groups. Results obtained in the POMS Scale, testing components of basic mood, do not differ statistically analyzed groups. In both groups were not observed changes in categories "dominance", "frankness" "Self-control" in the Giessen test. In the categories "basic mood", "social resonance", "social possibilities" was noted significant improvement. Here, were not found statistical differences between groups B and P, also.

Results obtained in the group B after 6 months do not differ significantly differ from obtained in the group P. The detailed results are shown in tables 8, 9, 10, 11 and 12 and figures 4, 5, 6, 7 and 8.

Table 8. Life Quality Scale – chosen subscales concerning psychic and sexual life

Symptom	Scores in consecutive months of therapy – group B							Scores in consecutive months of therapy – group P						
	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Lack of personal life satisfaction	3.18 ±1.63	3.20 ±1.58	3.18 ±1.52	3.21 ±1.60	3.26 ±1.56	3.24 ±1.58	3.24 ±1.60	3.19 ±1.48	3.19 ±1.45	3.23 ±1.52	3.23 ±1.50	3.20 ±1.59	3.17 ±1.43	3.20 ±1.56
Unrest and irritation feeling	4.20 ±1.78	4.14 ±1.69	4.02 ±1.71	3.88 ±1.69	3.52 ±1.65	3.18 ±1.47	2.87 ±1.39	3.98 ±1.81	4.04 ±1.86	4.01 ±1.78	3.97 ±1.73	3.86 ±1.72	3.64 ±1.62	3.03 ±1.47
Irritability,	3.69 ±1.73	3.64 ±1.74	3.46 ±1.65	3.23 ±1.59	3.34 ±1.52	3.66 ±1.71	3.42 ±1.68	3.68 ±1.72	3.59 ±1.78	3.61 ±1.64	3.57 ±1.48	3.39 ±1.52	3.53 ±1.58	3.46 ±1.61
Tearfulness	3.01 ±1.43	2.71 ±1.28	2.46 ±1.22	2.27 ±1.03	2.03 ±0.83	1.98 ±0.89	1.73 ±0.82	3.05 ±1.46	3.03 ±1.38	2.86 ±1.27	2.38 ±1.12	2.18 ±1.05	1.93 ±0.76	1.87 ±0.61
Fear or panic attacks	3.18 ±1.52	3.07 ±1.42	2.88 ±1.49	2.65 ±1.14	2.38 ±1.12	2.03 ±0.97	1.79 ±0.82	2.99 ±1.43	2.86 ±1.38	2.84 ±1.38	2.59 ±1.24	2.29 ±1.06	1.78 ±0.87	1.75 ±0.64
Memory weakness	2.78 ±1.32	2.54 ±1.25	2.36 ±1.16	2.29 ±1.03	2.02 ±0.93	1.86 ±0.75	1.84 ±0.85	2.81 ±1.37	2.69 ±1.28	2.66 ±1.31	2.48 ±1.22	2.29 ±1.03	2.03 ±0.99	1.88 ±0.85
Concentration difficulties	3.01 ±1.42	2.88 ±1.41	2.74 ±1.26	2.23 ±1.07	2.22 ±1.01	2.14 ±0.84	1.93 ±0.87	3.07 ±1.42	3.09 ±1.25	2.86 ±1.32	2.79 ±1.29	2.32 ±1.14	2.11 ±1.01	1.90 ±0.75
Reduced self-satisfaction,	2.87 ±1.32	2.84 ±1.29	2.55 ±1.21	2.59 ±1.23	2.32 ±1.18	2.02 ±0.93	1.84 ±0.82	2.69 ±1.28	2.72 ±1.28	2.69 ±1.22	2.64 ±1.29	2.59 ±1.18	2.31 ±1.12	1.92 ±0.83
Depression feeling	3.21 ±1.46	3.03 ±1.42	2.71 ±1.31	2.24 ±1.08	2.02 ±0.86	1.95 ±0.82	1.86 ±0.73	3.34 ±1.32	3.29 ±1.07	3.31 ±1.04	3.02 ±1.39	2.53 ±1.23	2.01 ±0.93	1.90 ±0.82
Impatience towards other persons	2.93 ±1.84	2.79 ±1.88	2.84 ±1.63	2.89 ±1.38	2.88 ±1.32	2.88 ±1.42	2.86 ±1.26	2.97 ±1.41	2.86 ±1.32	2.86 ±1.39	2.93 ±1.41	2.79 ±1.32	2.82 ±1.36	2.83 ±1.38
Solitude desire	2.75 ±1.32	2.54 ±1.21	2.51 ±1.14	2.14 ±0.84	1.97 ±0.82	1.88 ±0.73	1.94 ±0.77	2.89 ±1.41	2.88 ±1.32	2.74 ±1.26	2.68 ±1.22	2.19 ±1.03	2.24 ±1.02	2.02 ±0.83
Interest loss	2.67 ±1.21	2.43 ±1.18	2.12 ±0.96	2.05 ±0.73	1.75 ±0.62	1.57 ±0.69	1.32 ±0.59	2.49 ±1.22	2.52 ±1.19	2.32 ±1.12	2.29 ±1.08	2.09 ±0.94	1.67 ±0.82	1.42 ±0.69
Sleeplessness	3.27 ±1.51	3.12 ±1.46	2.78 ±1.32	2.31 ±1.14	2.06 ±0.78	1.74 ±0.86	1.71 ±0.82	3.18 ±1.52	3.16 ±1.48	3.24 ±1.54	3.12 ±1.46	2.77 ±1.32	2.29 ±1.12	1.82 ±0.86
Fatigue feeling	3.47 ±1.66	3.12 ±1.47	3.10 ±1.69	2.59 ±1.22	2.54 ±1.18	2.01 ±0.89	1.92 ±0.75	3.53 ±1.43	3.46 ±1.35	3.39 ±1.52	3.08 ±1.43	2.89 ±1.29	2.49 ±1.22	2.18 ±0.94
Reduced life energy	3.22 ±1.52	3.01 ±1.43	2.74 ±1.32	2.29 ±1.08	1.89 ±0.84	1.83 ±0.63	1.86 ±0.68	3.13 ±1.43	3.16 ±1.38	2.94 ±1.36	2.73 ±1.27	2.48 ±1.17	2.08 ±1.09	1.93 ±1.12
Change of sexual drive	2.78 ±1.27	2.85 ±1.26	2.49 ±1.18	2.69 ±1.31	2.71 ±1.01	2.59 ±1.03	2.62 ±1.12	2.71 ±1.04	2.77 ±1.09	2.68 ±1.17	2.66 ±1.19	2.66 ±1.19	2.64 ±1.08	2.66 ±1.09
Vagina dryness during sexual intercourse	2.37 ±1.12	2.21 ±1.08	2.14 ±1.22	2.15 ±1.18	2.04 ±1.05	1.98 ±1.14	1.95 ±1.18	2.29 ±1.06	2.29 ±1.02	2.19 ±1.12	2.21 ±1.05	1.94 ±1.02	1.94 ±0.94	1.91 ±0.96
Sexual intercourse avoidance	3.13 ±1.48	3.27 ±1.56	3.18 ±1.32	3.18 ±1.38	3.24 ±1.28	2.95 ±1.39	2.97 ±1.36	2.89 ±1.34	2.95 ±1.28	2.82 ±1.25	2.98 ±1.27	2.98 ±1.27	2.91 ±1.32	2.86 ±1.24
Loss interest in sex	2.79 ±1.35	2.85 ±1.37	2.69 ±1.22	2.78 ±1.28	2.83 ±1.24	2.76 ±1.31	2.82 ±1.27	2.58 ±1.22	2.65 ±1.27	2.72 ±1.32	2.67 ±1.27	2.64 ±1.28	2.59 ±1.17	2.52 ±1.14

Table 9. BSRDS changes – average results

Group	Scores in consecutive months of therapy						
	0	1	2	3	4	5	6
B	13.67 ±8.77	12.48 ±7.83	11.48 ±6.85	10.15 ±5.86	9.87 ±4.83	9.63 ±4.72	9.32 ±4.26
P	14.03 ±7.36	14.12 ±7.12	13.84 ±6.88	13.72 ±6.78	12.46 ±5.94	11.26 ±5.28	10.02 ±4.87

Figure 4. Changes dynamics in BSRDS

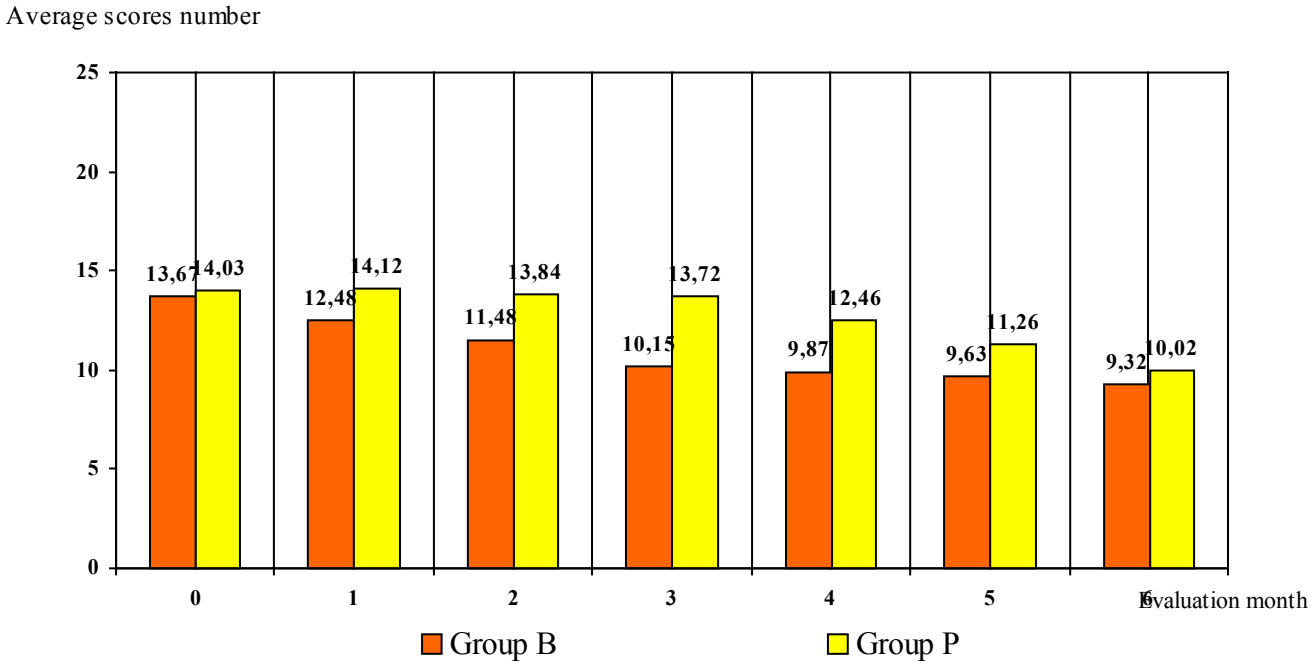


Table 10 Changes in Beck's Self-Assesment Rate Depression Scale – analysis of chosen symptoms

Symptom	Scores in consecutive therapy months – group B							Scores in consecutive therapy months – group P						
	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Depression	6.32 ±5.24	6.02 ±4.29	5.63 ±5.03	5.58 ±4.68	5.24 ±4.68	5.07 ±4.62	4.78 ±4.25	5.98 ±4.78	6.07 ±4.62	6.06 ±4.73	5.93 ±4.85	5.79 ±4.79	5.32 ±4.63	4.96 ±4.52
Reduction of complex activity	2.24 ±1.58	2.17 ±1.79	2.04 ±1.69	1.86 ±0.98	1.73 ±0.96	1.66 ±0.94	1.68 ±1.04	2.08 ±1.65	2.13 ±1.54	2.05 ±1.56	2.02 ±1.58	1.88 ±1.02	1.72 ±1.08	1.65 ±1.12
Anxiety	0.92 ±0.72	0.78 ±0.70	0.74 ±0.64	0.66 ±0.58	0.63 ±0.49	0.58 ±0.47	0.58 ±0.47	0.89 ±0.72	0.91 ±0.85	0.86 ±0.75	0.84 ±0.68	0.77 ±0.70	0.65 ±0.59	0.60 ±0.50
Somatisation,	0.94 ±0.56	0.90 ±0.58	0.84 ±0.54	0.74 ±0.56	0.62 ±0.48	0.64 ±0.51	0.58 ±0.50	0.95 ±0.51	0.97 ±0.54	0.91 ±0.56	0.93 ±0.57	0.71 ±0.49	0.61 ±0.53	0.58 ±0.51
Circadian rhythm disturbances	2.48 ±1.23	2.39 ±1.28	2.37 ±1.22	2.32 ±1.26	2.16 ±1.14	1.83 ±1.02	1.36 ±1.06	2.55 ±1.83	2.51 ±1.22	2.48 ±1.64	2.51 ±1.22	2.39 ±1.03	1.74 ±1.16	1.48 ±1.02

Table 11. Changes in POMS Scale

Studied feature	Scores in consecutive therapy months – group B							Scores in consecutive therapy months – group P						
	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Anger	17.39 ±7.04	17.06 ±6.58	16.58 ±7.14	13.32 ±6.52	12.58 ±5.84	11.64 ±5.92	10.86 ±5.08	17.52 ±8.14	17.28 ±7.59	16.83 ±7.19	16.77 ±8.12	14.28 ±6.56	12.03 ±5.82	11.09 ±5.03
Tension	14.68 ±5.26	13.29 ±6.11	11.68 ±5.38	10.27 ±4.87	9.74 ±4.23	8.57 ±4.52	8.53 ±3.90	14.04 ±5.83	13.88 ±5.92	13.73 ±5.31	13.10 ±5.40	11.57 ±4.82	9.86 ±4.17	9.03 ±4.02
Depression	18.93 ±9.21	18.02 ±9.03	16.60 ±8.11	14.57 ±7.22	13.72 ±6.36	11.83 ±5.48	10.62 ±4.70	17.96 ±8.51	17.72 ±8.30	17.06 ±8.12	16.39 ±7.57	15.64 ±7.46	12.71 ±5.90	11.02 ±5.82
Vigor	12.83 ±6.23	11.55 ±5.14	14.02 ±6.80	14.79 ±7.02	14.73 ±6.98	14.81 ±7.18	14.90 ±7.24	12.08 ±5.83	12.14 ±6.01	11.83 ±5.10	12.82 ±6.28	13.52 ±6.58	14.07 ±6.98	14.35 ±7.14
Confusion	13.06 ±7.01	12.89 ±7.12	13.12 ±6.88	12.84 ±6.34	14.83 ±7.23	12.66 ±6.06	11.20 ±5.92	14.68 ±7.22	14.21 ±7.04	12.61 ±6.21	11.85 ±5.17	12.96 ±6.35	13.13 ±6.52	12.67 ±6.28
Fatigue	10.37 ±5.05	9.84 ±4.34	8.45 ±4.10	7.68 ±3.35	7.14 ±3.20	6.84 ±3.03	6.41 ±3.08	9.52 ±4.24	9.38 ±4.16	9.56 ±4.61	9.06 ±4.05	8.24 ±3.96	7.11 ±3.57	6.35 ±3.42

Figure 5. Changes in POMS Scale after 6 months of therapy – group B

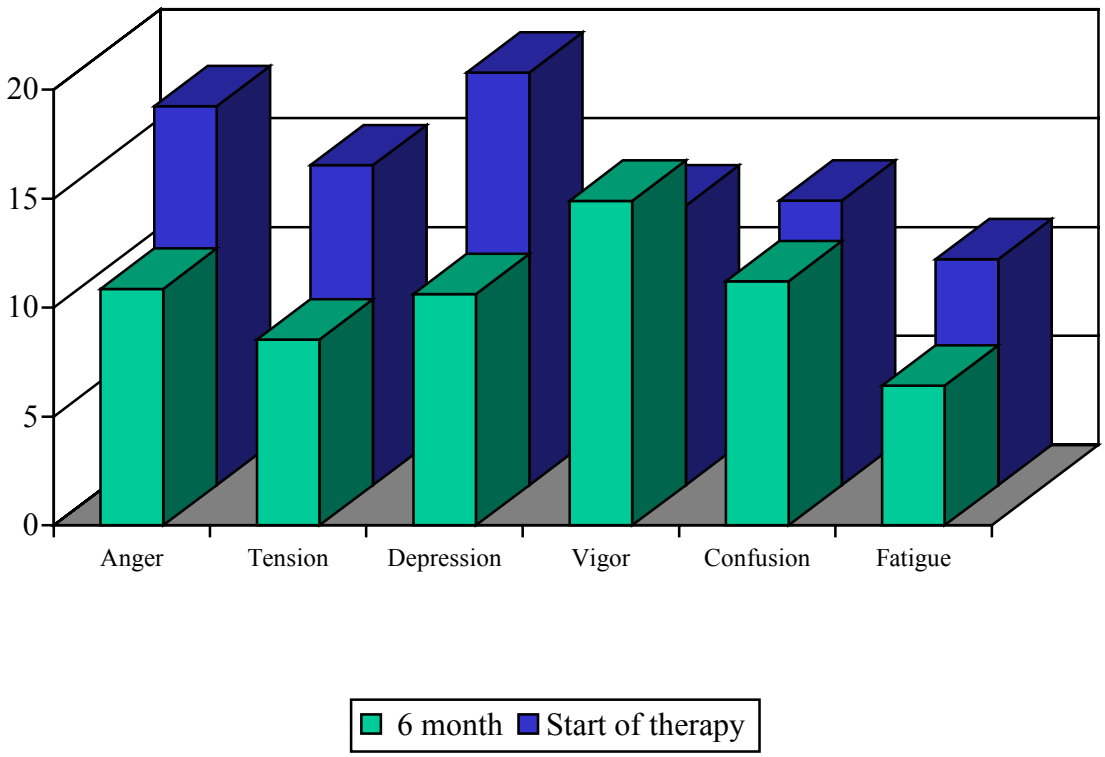


Figure 5. Changes in POMS Scale after 6 months of therapy – group P

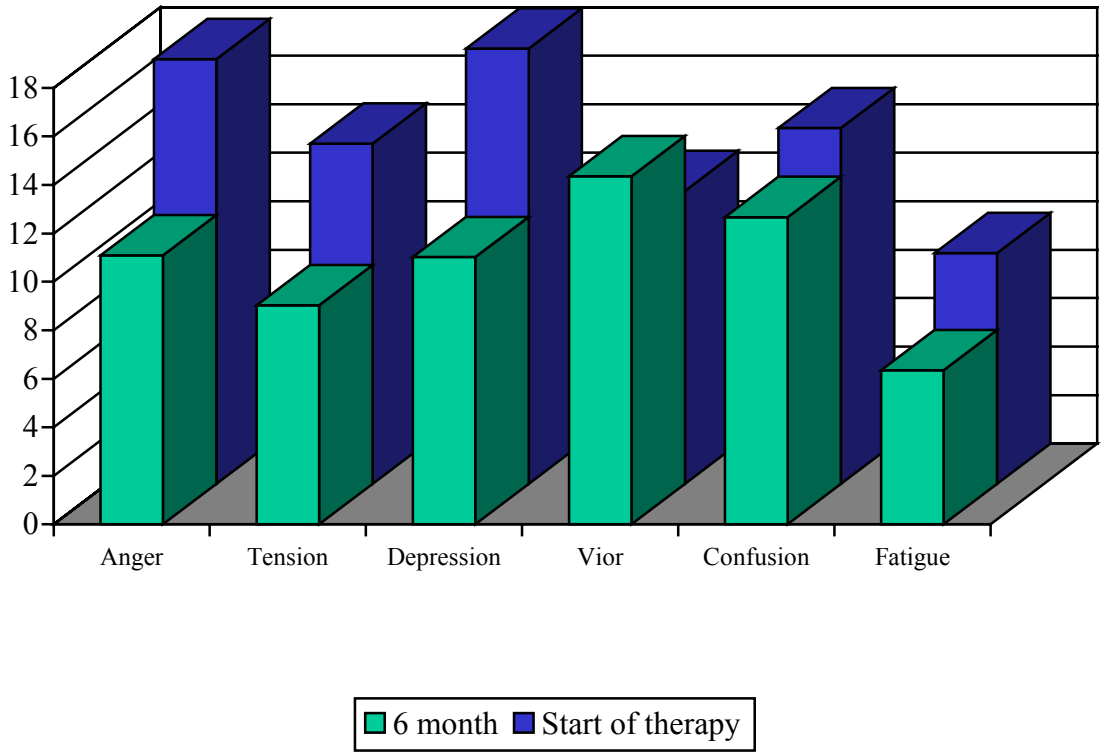


Table 12. Giessen test – Changes during therapy

Studied feature	Scores in consecutive therapy months – group B							Scores in consecutive therapy months – group P						
	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Dominance	3.56 ±1.38	3.59 ±1.42	3.56 ±1.40	3.73 ±1.40	3.62 ±1.76	3.69 ±1.84	3.61 ±1.76	3.38 ±1.62	3.26 ±1.58	3.35 ±1.46	3.38 ±1.55	3.45 ±1.62	3.43 ±1.60	3.48 ±1.66
Frankness	3.02 ±1.47	3.08 ±1.51	3.11 ±1.56	3.09 ±1.55	3.22 ±1.59	3.19 ±1.57	3.20 ±1.55	3.14 ±1.52	3.10 ±1.50	3.14 ±1.58	3.15 ±1.60	3.08 ±1.57	3.16 ±1.57	3.19 ±1.59
Self-control	3.86 ±1.59	3.90 ±1.64	3.89 ±1.78	3.93 ±1.60	4.04 ±1.82	4.15 ±1.84	4.17 ±1.88	3.79 ±1.76	3.81 ±1.79	3.78 ±1.72	3.82 ±1.81	3.89 ±1.84	3.91 ±1.85	3.93 ±1.89
Basic mood	3.02 ±1.45	3.14 ±1.51	3.23 ±1.57	3.47 ±1.63	3.74 ±1.69	3.95 ±1.71	3.98 ±1.75	3.06 ±1.49	3.02 ±1.43	3.11 ±1.51	3.13 ±1.55	3.58 ±1.62	3.66 ±1.73	3.89 ±1.78
Social resonance	3.72 ±1.62	3.76 ±1.66	3.91 ±1.70	4.12 ±1.63	4.33 ±1.68	4.36 ±1.65	4.36 ±1.71	3.63 ±1.72	3.68 ±1.73	3.65 ±1.58	3.73 ±1.74	3.83 ±1.83	3.89 ±1.86	4.08 ±1.88
Social possibilities	3.96 ±1.83	3.99 ±1.85	4.05 ±1.74	4.16 ±1.78	4.17 ±1.79	4.26 ±1.84	4.24 ±1.80	3.92 ±1.86	3.90 ±1.83	3.98 ±1.88	3.98 ±1.81	4.07 ±1.92	4.18 ±1.96	4.21 ±1.93

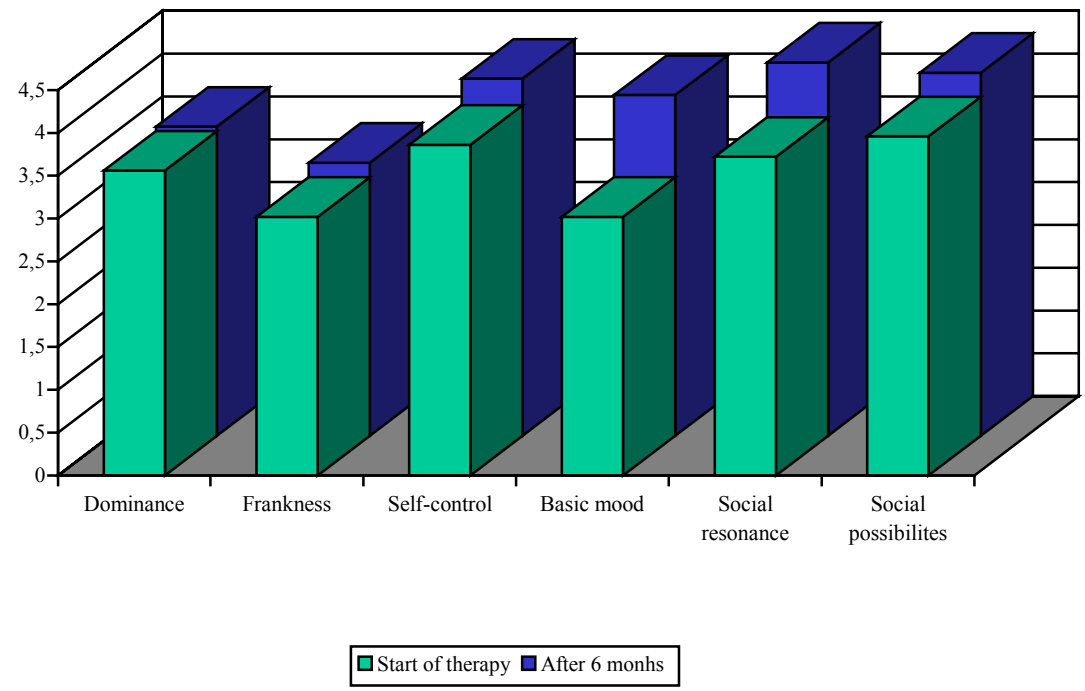
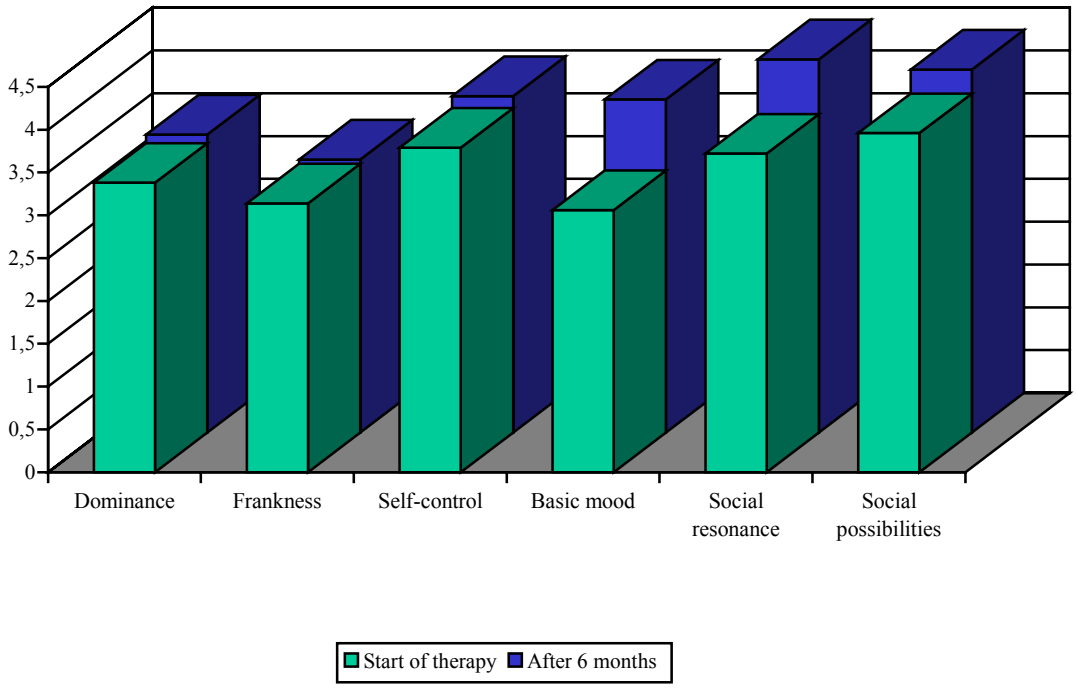


Figure 8. Giessen Test – changes during 6 months therapy – group P



Anti-depression effect evaluation in persons with diagnosed depression disturbances

Clinically significant depression symptoms evaluated with Beck's self-assesment scale were found in 68 persons (34.7% of population qualified into study). 12 or more scores in Beck's self-assesment scale were considered as a threshold of significant depression symptoms. The major depression (F32 or F33 acc. ICD-10) was diagnosed in 30 of them (10 in the group B, 20 in the group P), dystymia in 19 -F34 (6 i group B, 13 w group P), 18 persons were qualified as category named: depression and anxiety mixed disorder, that is F41.2 acc. ICD-10 (8 in the group B, 10 in the group P). Psychiatric examination in one person (group P) did not confirm depression disorder. Significant clinical depression symptoms found during the patient qualification into studies occurred with the similar frequency (lack of significant difference) in both groups, that is in 14 persons of the group B (13.7%) and in 15 of the group P (15.0%). Depression disorders, which occurred during the study course were in noticed 38 women that is 10 of the group B and 28 of the group P. According these data depression disorders requiring treatment occurred less frequently in women which taken Klimakt-Heel preparation earlier. Chosen data according actual depression are shown in the table 13. The Ignatia Homaccord preparation in dose 3x10 drops was included into the therapy in 67 persons, to evaluation of depression symptoms was included the 17 score version of Hamilton's Scale (HDRS) and subjective evaluation of the therapy results by physician and patient. Evaluation of depression symptoms were done on start of therapy and after 1, 2, 4 and 6 week of therapy. Patients with depression from the studied group were called B1 and from the control group P1.

Average reduction of HDRS scores was 57.05% in the group B1 and 55.68% in the group P1. HDRS scores reduction exceeding 50% were obtained in 70.83% persons of the group B1 and 65.12% of the group P1. Differences are not statistically significant. Similar results were obtained in the Beck's Questionnaire.

During administration the Ignatia Homaccord preparation were observed progressive changes of the clinical condition of patients with depression. Significant improvement ($p<0.05$)is found after first week of therapy already. The improvement index reached 48.4% in the group B and 50.9% in the group P1 after 28 days, respectively 57.05% and 55.68% after 42 days. Differences between 28 and 42 day of therapy are not statistically significant in both groups.

Detailed results are shown in tables 14, 15, 16 and 17 and figures 9 and 10.

Table 18 shows dynamics of changes of improvement index with taking under consideration patient division according to therapy effect in 42 day. Separated groups differ significantly in symptoms reduction rate in consecutive days of evaluation – persons, in which therapy gives considerable improvement obtained the higher symptoms reduction in 7 and 14 therapy day already. Data showed in the table concern all persons with depression (group B+P).

Table 13. Chosen present depression features

Feature	Group B1	Group P1
1. Age of falling ill	45.5±16.2	44.3±14.2
2. Disease duration (years)	5.6±5.2	5.2±4.8
3. Present depression duration before the start of therapy (months)	5.4±6.5	6.2±6.7
4. Depression form - major depression (F33, F32) - dystymia (F34) - depression and anxiety mixed disorder (F41.2)	 10 6 8	 20 13 10
5. Depression syndrome intensity acc. HDRS	21.63±2.39	22.72±3.01

Table 14. Ignatia Homaccord– anti-depressive effect evaluation in the studied group (B1)

Evaluation criterion	Number of persons (%) n=24
1 . Beck's self-assessment depression scale	
scores reduction higher than 75%	2 (8.33%)
scores reduction higher than 50%	17 (70.83%)
scores reduction lower than 50%	7 (29.17%)
2. Hamilton's Scale (HDRS)	
scores reduction higher than 75%	3 (12.50%)
scores reduction higher than 50%	17 (70.83%)
scores reduction lower than 50%	7 (29.17%)
3. Reporting physician evaluation	
very good effect	4 (16.67%)
good effect	10 (41.67%)
moderate effect	5 (20.83%)
weak effect/ deterioration	5 (20.83%)
4. Subjective evaluation of studied persons	
very good effect	5 (20.83%)
good effect	12 (50.00%)
moderate effect	3 (12.50%)
weak effect/ deterioration	4 (16.67%)
5. CGI	
Total effects regression of symptoms,	5 (20.83%)
Partial regression of symptoms,	11 (45.83%)
Slight improvement;	3(12.50%)
Without changes/deterioration	5 (20.83%)

Table 15. Ignatia Homaccord– anti-depressive effect evaluation in the studied group (P1)

Evaluation criterion	Number of persons (%) n=43
1 . Beck's self-assessment depression scale	
scores reduction higher than 75%	4 (9.30%)
scores reduction higher than 50%	28 (65.12%)
scores reduction lower than 50%	15 (34.88%)
2. Hamilton's Scale (HDRS)	
scores reduction higher than 75%	6 (13.95%)
scores reduction higher than 50%	26 (60.47%)
scores reduction lower than 50%	17 (39.53%)
3. Reporting physician evaluation	
very good effect	7 (16.28%)
good effect	23 (53.49%)
moderate effect	7 (16.28%)
weak effect/ deterioration	6 (13.95%)
4. Subjective evaluation of studied persons	
very good effect	11 (25.58%)
good effect	19 (44.19%)
moderate effect	7 (16.28%)
weak effect/ deterioration	6 (13.95%)
5. CGI	
Total effects regression of symptoms,	9 (20.93%)
Partial regression of symptoms,	21 (48.84%)
Slight improvement;	6 (13.95%)
Without changes/deterioration	7 (16.28%)

Table 16 Clinical condition changes dynamics acc. HDRS

Group	Feature	Consecutive day of therapy				
		0	7	14	28	42
B1	Number of persons(n)	24	24	24	24	24
	Average HDRS score number	21.63±2.39	16.88±3.47	13.75±2.98	11.17±2.15	9.29±2.56
	Score difference in comparison to day „0”	-	4.75	7.88	10.46	12.34
	Improvement index	-	21.9%	36.4%	48.4%	57.1%
P1	Number of persons(n)	43	43	43	43	43
	Average HDRS score number	22.72±3.01	18.88±3.35	16.58±3.83	11.16±2.17	10.07±2.65
	Score difference in comparison to day „0”	-	3.84	6.14	11.56	12.65
	Improvement index	-	16.9	27.0%	50.9%	55.7%

Table 17 Changes in BSRDS – average results

Group	Scores in consecutive days of therapy				
	0	7	14	28	42
B1	27.33 ±7.66	22.13 ±6.12	18.54 ±4.37	13.46 ±3.82	11.13 ±3.47
P1	28.58 ±6.94	25.67 ±5.46	21.19 ±4.49	14.79 ±2.47	10.93 ±2.76

In comparison with previous evaluation in 7, 14, 28 day in both scales, $p<0.05$

Figure 9. Dynamics of average HDRS values changes in both groups

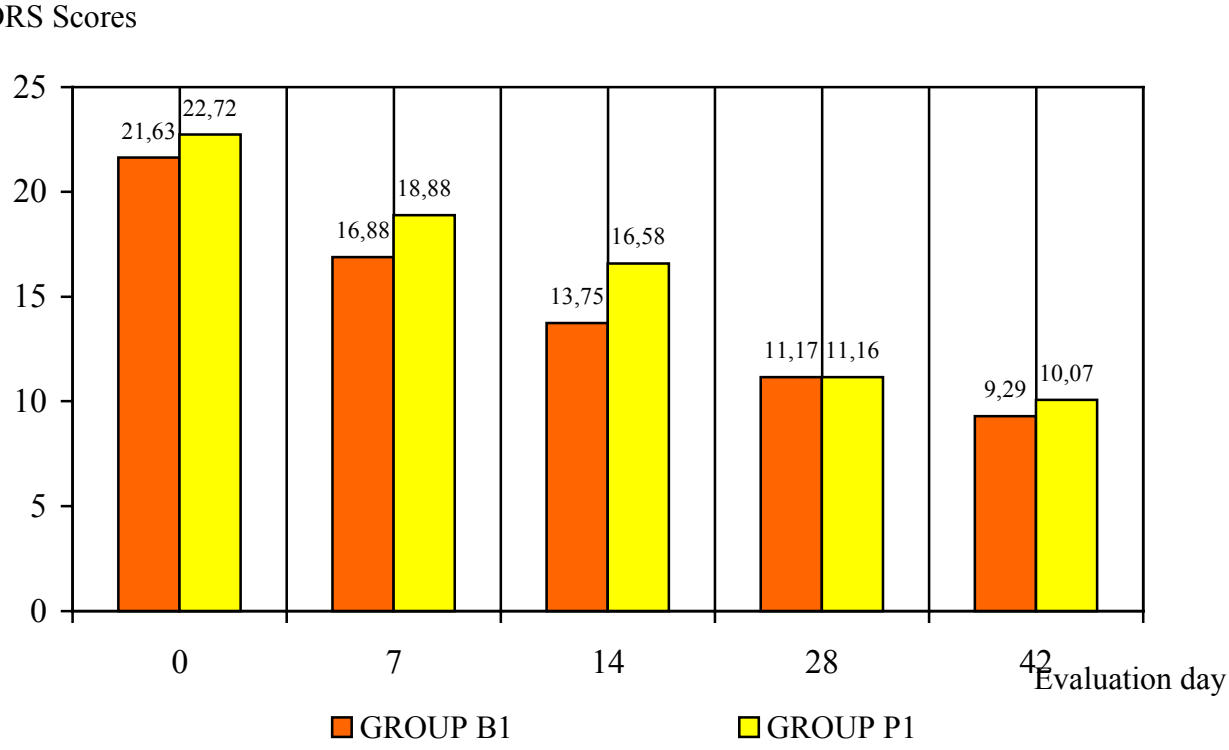
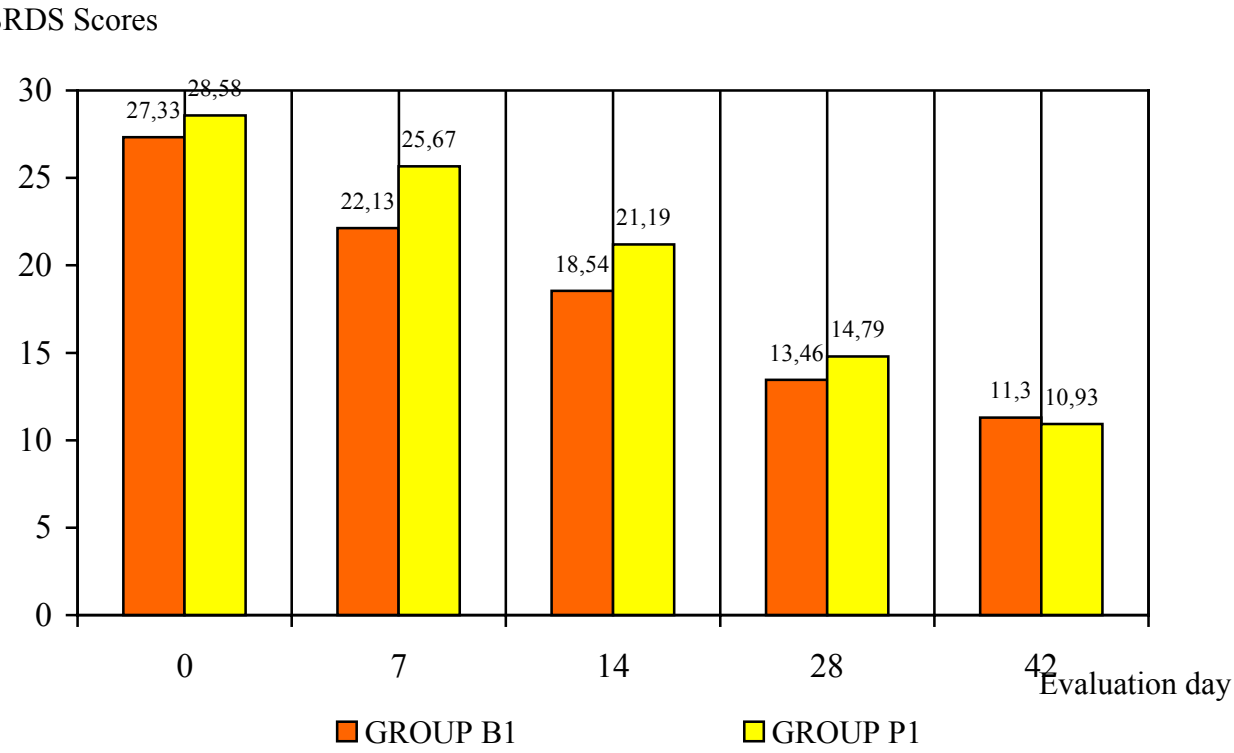


Figure 10. Dynamics of average BSDRS values changes in both groups



In comparison with previous evaluation in 7, 14, 28 day in both scales, $p<0.05$

Table 18. Depression symptoms regression depending of final effect.

Therapeutic effect acc. CGI	Average scores number in day „0”	Difference in HDRS score number (acc. day „0”)			
		7 day	14 day	28 day	42 day
1. Total regression of symptoms	22.6±3.26	6.4±4.45 c	12.8±3.01 c	16.7±3.02 b c	19.0±2.29 a b c
2. Partial regression of symptoms	23.1±4.02	5.1±3.87	8.9±2.23 c	13.5±2.23 b c	15.2±3.26 b c
3. Slight improvement	21.2±2.26	4.5±2.76	6.6±4.61	6.7±2.46	6.9±3.46 c
4. Lack of improvement. deterioration	20.6±3.26	0.81±2.16	2.6±2.89	3.2±3.12	2.9±3.14

a: in comparison with 2, $p<0.05$

b: in comparison with 3, $p<0.05$

c: in comparison with 4, $p<0.05$

Adverse symptoms evaluation

Adverse symptoms were evaluated and categorized on the basis of ailments subjective reported by studied persons. Results are shown on figures and tables. The adverse symptoms occurred in both groups with different frequency. In the group P number and frequency of symptoms was considerably higher during evaluation after the first and second month of therapy. In subsequent measurements difference between group B and P decreased but was still significant. As it was mentioned earlier, 8 persons (9.36% of persons included in therapy) of the group P did not finish study because of adverse effects occurrence. Because of that in further part of the study were evaluated persons who completed the project, only.

Most often reported adverse effects were spotting, breast tension and tenderness, appetite increase, feeling of being full, headache, exacerbation of varices symptoms. In both groups some of symptoms occurred before starting the therapy, then in the group B they can be concern as associated symptoms, independent of used therapy. In the group P relationship was considerable. E.g. percentage of women reporting headaches increased from 13.58% before the therapy up to 23.46% after first month of HRT. Other reported adverse symptoms (acne, nausea) occurred considerably rare and in group P only. Adverse symptoms of psychic sphere (irritability, anxiety, emotional instability, depressive mood, sleeplessness, poor concentration) were not evaluated because of difficulties of their interpretation. They occur in the Affective Symptoms Syndrome in women with depression and neurosis disturbances. In such situation is difficult to describe what is an adverse symptom and what is a disease symptom. Results are shown in tables 19 – 24 and figures 11-16.

Table19. Adverse symptoms

Spotting		
Month of evaluation	Number of persons (%)	
	Group B n=97	Group P n=81
0	0 (0%)	0 (0%)
1	4 (4.12%)	24 (29.63%)
2	1 (1.03%)	21 (25.92%)
3	0 (0%)	17 (20.99%)
4	3 (3.09%)	15 (18.52%)
5	1 (1.03%)	16 (19.75%)
6	0 (0%)	14 (17.28%)

Figure 11. Adverse symptoms - spotting

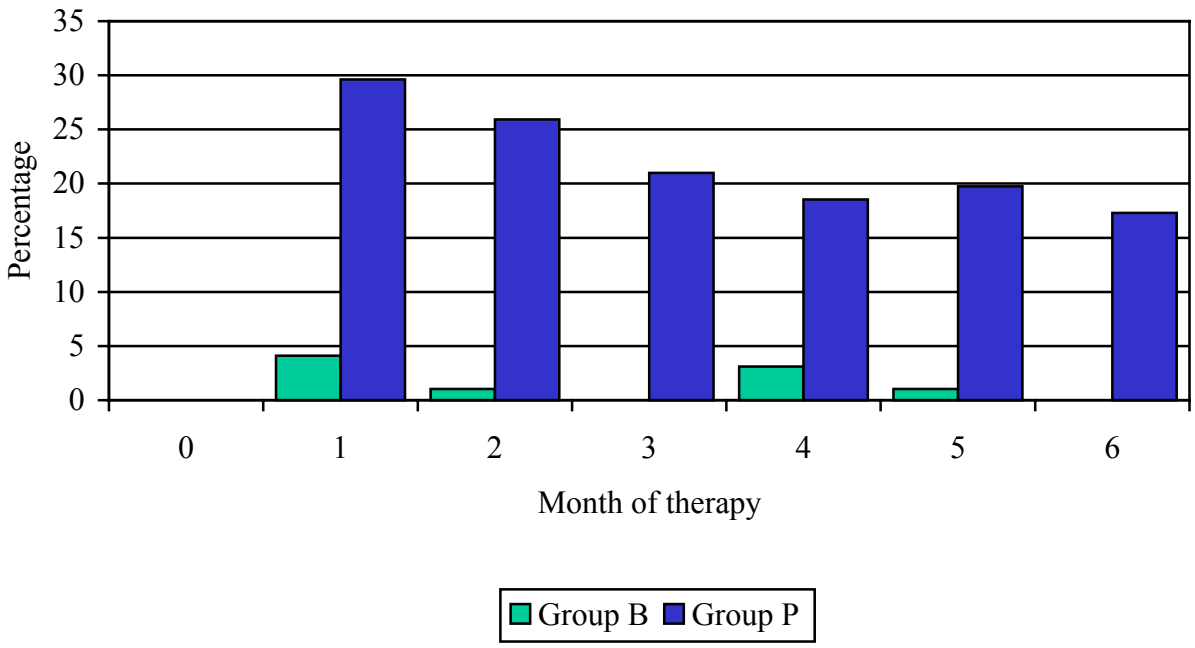


Table 20. Adverse symptoms

Mastalgia		
Month of evaluation	Number of persons (%)	
	Group B, n=97	Group P, n=81
0	0 (0%)	0 (0%)
1	2 (2.06%)	30 (37.04%)
2	0 (0%)	24 (29.63%)
3	0 (0%)	12 (14.81%)
4	1 (1.03%)	11 (13.58%)
5	0 (0%)	13 (16.05%)
6	0 (0%)	12 (14.81%)

Figure 12. Adverse symptoms - mastalgia

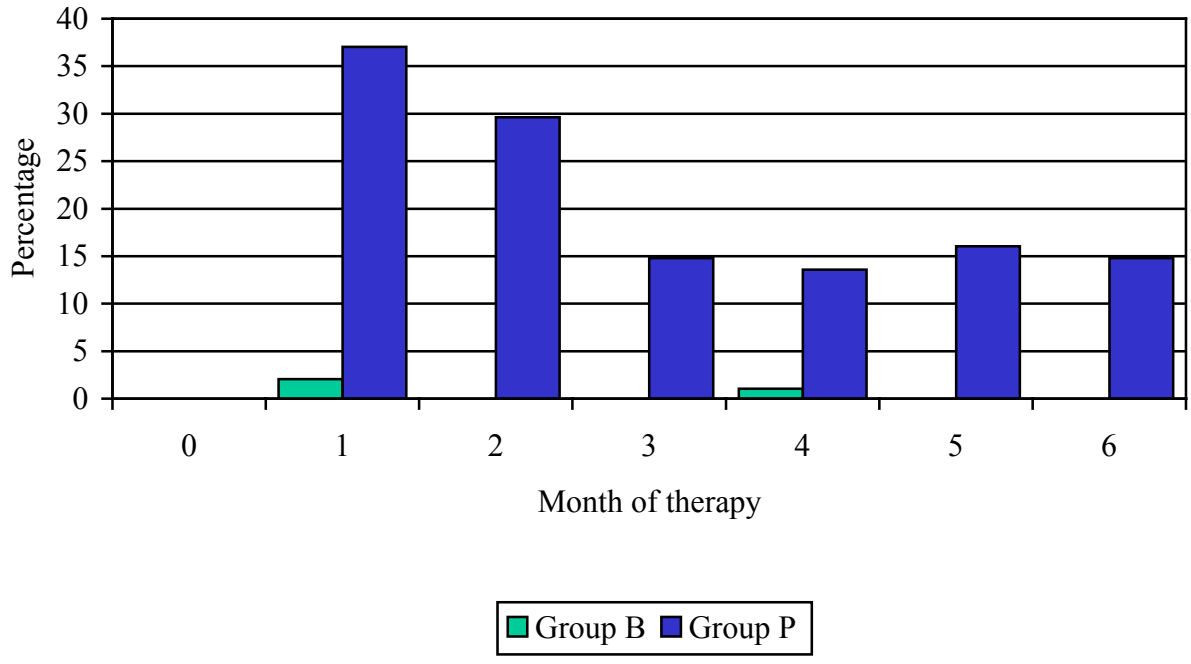


Table 21. Adverse symptoms

Appetite growth		
Month of evaluation	Number of persons (%)	
	Group B, n=97	Group P, n=81
0	0 (0%)	0 (0%)
1	1 (1.03%)	17 (20.99%)
2	0 (0%)	19 (23.46%)
3	0 (0%)	12 (14.81%)
4	0 (0%)	11 (13.58%)
5	1 (1.03%)	9 (11.11%)
6	0 (0%)	9 (11.11%)

Figure 13. Adverse symptoms – appetite growth

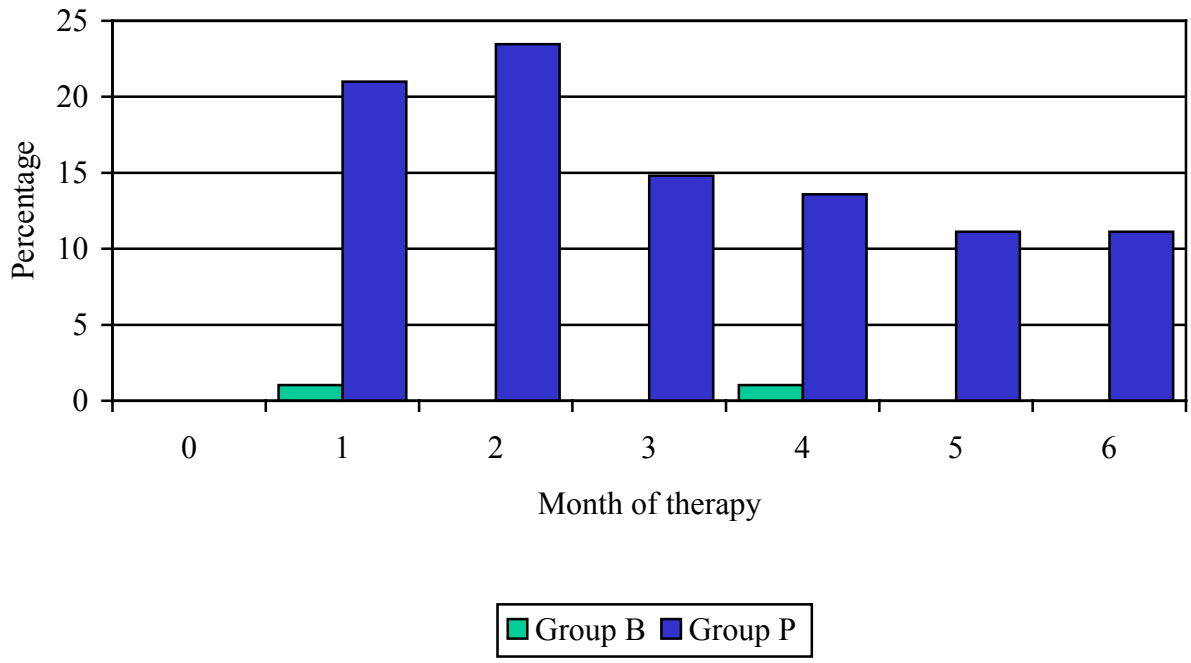


Table 22. Adverse symptoms

Fullness feeling		
Month of evaluation	Persons number (%)	
	Group B, n=97	Group P, n=81
0	6 (6.18%)	4 (4.94%)
1	6 (6.18%)	28 (34.57)
2	4 (4.12%)	24 (29.63%)
3	6 (6.18%)	21 (25.92%)
4	6 (6.18%)	11 (13.58%)
5	4 (4.12%)	13 (16.05%)
6	5 (5.15%)	11 (13.58%)

Figure 14. Adverse symptoms –fullness feeling

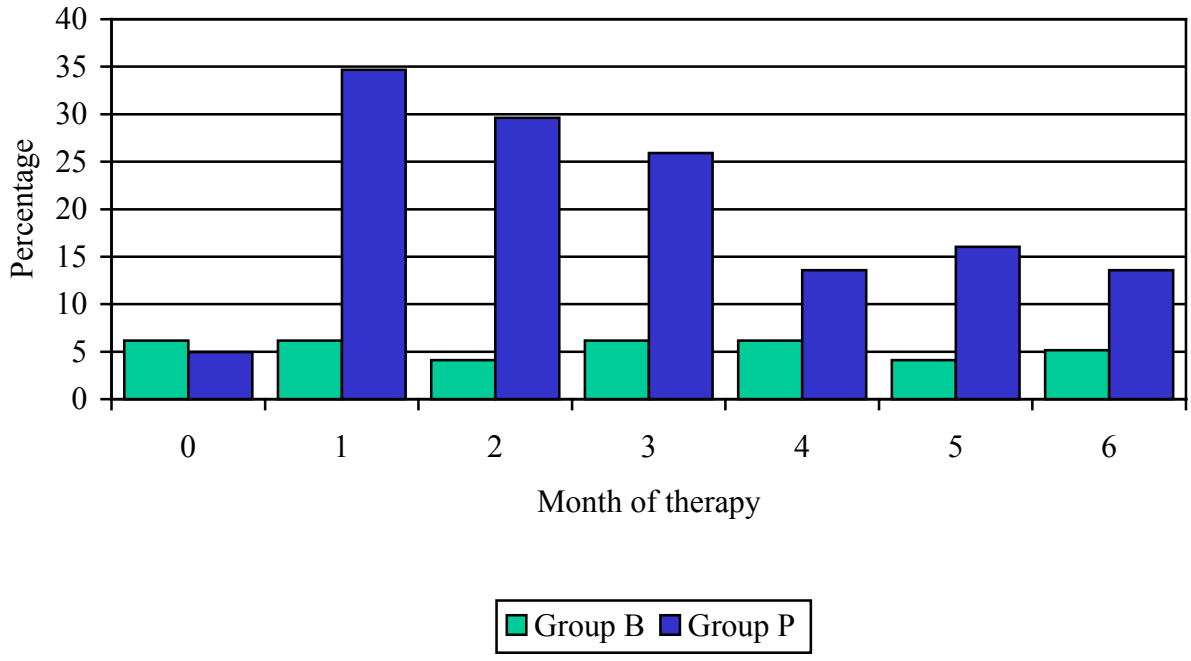


Tabela 23. Adverse symptoms

Headaches		
Evaluation month	Number of persons (%)	
	Group B, n=97	Group P, n=81
0	14 (14.43%)	11 (13.58%)
1	11 (11.34%)	19 (23.46%)
2	8 (8.25%)	18 (22.22%)
3	6 (6.18%)	13 (16.05%)
4	5 (5.15%)	12 (14.81%)
5	5 (5.15%)	10 (12.34%)
6	4 (4.12%)	10 (12.34%)

Figure 15. Adverse symptoms – headaches

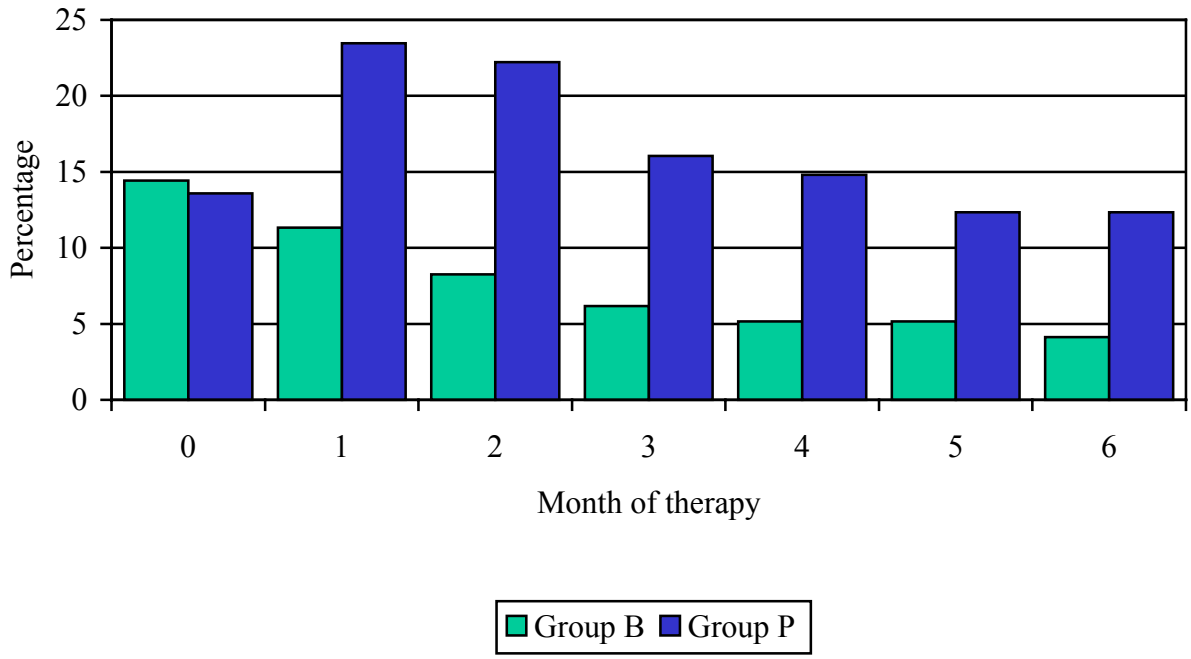
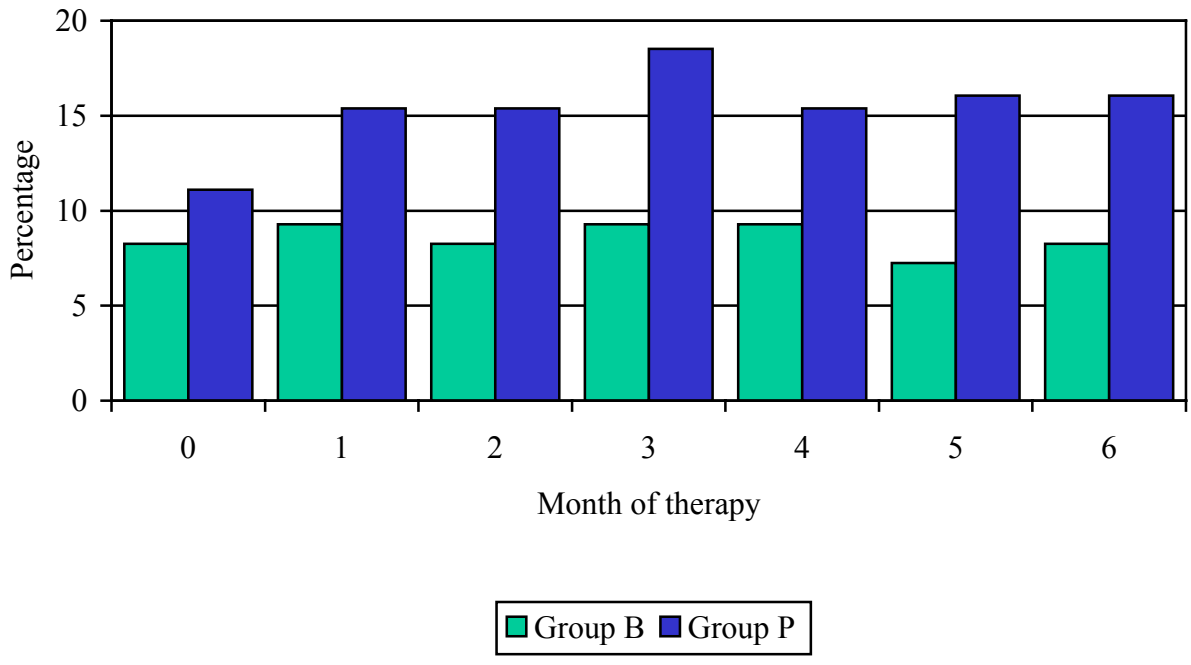


Table 24. Adverse symptoms

Exacerbation of varices symptoms		
Evaluation month	Number of persons (%)	
	Group B, n=97	Group P, n=81
0	8 (8.25%)	9 (11.11%)
1	9 (9.28%	14 (15.38%)
2	8 (8.25%)	14 (15.38%)
3	9 (9.28%	15 (18.52%)
4	9 (9.28%	14 (15.38%)
5	7 (7.25%)	13 (16.05%)
6	8 (8.25%)	13 (16.05%)

Figure 16. Adverse symptoms – varices symptoms



Results description

Therapeutic effects in scope of affective symptoms

Obtained therapeutic effects in both groups should be recognized as satisfactory. They are not surprising and confirm observations of outclinic practice and are consistent with scientific reports, at least referring to HRT. Considerable improvement in scope of decrease of number and intensity of affective symptoms in both groups, with relatively low and slightly intense adverse symptoms is consistent with literature data, up to now (25, 26).

Evaluation of chosen psychic and sexual life aspects

During the six month therapy with the Klimakt-Heel preparation in evaluation of patients of the B group was noted improvement in psychic well-being mainly according raise of mood. Results of all scales confirm significant drop of intensity of different symptoms connected with depression. Particularly is decreased anxiety, fear, increased self-acceptance, biological rhythms structure reaches balance. Improvement is noticed in cognitive functions, first of all the memory function. Similar results were obtained in group P also, but there were more frequent and longer maintained adverse symptoms.

Obtained results concerning the HRT are consistent with scientific reports. There is found positive effect of HRT, on chosen physical aspects during the long-term therapy. For example during three months therapy with a tibolon in patients evaluation was improvement in psychic well-being, concerning mostly mood. All scales confirm decrease of intensity of different symptoms connected with depression. Particularly is decreased anxiety and fear, self-acceptance level increase, biological rhythms structure reaches balance. In the cited study were improved cognitive functions as well, mainly memory. Even better results were obtained after the six month therapy (22).

It is noticeable, that changes observed by patients do not concern area connected with self-perception in the interpersonal context. It is strongly noticeable in sexual sphere; although was found significant potential improvement of sexual life quality, because of vaginal dryness decrease, the women did not observed increased interest in sex and significant sexual drive difference. It can be connected with maintained irritability and impatience in contacts with other people. It should be stressed that slight increased dissatisfaction of personal life can inhibit higher improvement of intimate life. These observations apply to both analysed groups.

Studied functions in large extent decide about life quality of women in perimenopausal period. Basing on obtained results we can state that used therapy in both analyzed groups significantly improve this quality.

Anti-depression effect in persons with diagnosed depression disturbances

Therapeutic effects obtained in persons with depression in both group should be evaluated as satisfactory. Obtained results are consistent with scientific reports so far. Associate therapy effects (Ignatia Homaccord + Klimakt Heel in the group B, Ignatia Homaccord + HRT in the group P1) were similar to known from literature (3, 15, 16, 17, 18). It should be underlined that there were not found differences between the Ignatia Homaccord preparation activity in associated therapy with the Klimakt Heel or the HRT and its effect in the monotherapy (20).

I would like to remind that depression disorders, which manifested themselves during studies, concerned 38 women that is 10 from the group B and 28 from the group P. According these data, depression disorders requiring therapy were considerably less frequent in women, who earlier used Klimakt-Heel preparation. It can mean, that the Klimakt-Heel preparation has prophylaxis influence that is decreasing on depression susceptibility or (and) increasing remission time in the case of relapse of disorders.

Adverse symptoms

In scope of adverse symptoms subjectively reported by respondents is found considerable difference between patients of both groups to the group B advantage. Peculiarly it applies to first three months of the therapy. The differences concern number of reported symptoms by patients and duration time during the study. It is highly probable that adverse symptoms were important in evaluation of chosen quality life aspects after 3rd month, patients of the group P had considerably worse results. It is fact, that in the group treated with the traditional HRT only one known cause of dropout were adverse symptoms. In the group B among 5 persons, which resigned, this cause of the dropout was not noted. Results according HRT are consistent with knowledge status so far (39).

Most authors agree that the hormonal therapy acceptation is dependent of number and intensity of adverse symptoms. Although good motivation and large interest in the hormonal therapy 76-81% patients using traditional the HRT drop out therapy before third year, that is before positive effects are reached according late menopause consequences (24, 39).

Results

1. Therapeutic effects as the result of the Klimakt Heel preparation use in the therapy of climacteric disturbances (so called affective symptoms) are comparable with results obtained using the classic HRT agents (lack of statistical difference). In both groups was obtained significant improvement in considerable larger group of patients.
2. In both groups (B and P) occurred the significant improvement in scope of chosen psychic aspects such as improvement of basic mood, self-assessment, better social functioning, improvement of cognitive function.
3. In the studied group (B) number of adverse symptoms and their spreading out were significantly lower than in the group P.
4. Depression disorders requiring the therapy were considerably rarely in women which used earlier the Klimakt-Heel preparation.
5. In groups with diagnosed depression (B1 i P1) was considerably antidepression effect obtained during Ignatia Homaccord preparation use.
6. There was not found the difference in the scope of antidepression effects between patients with depression who use the Ignatia Homaccord and the Klimakt Heel (group B1) concurrently and the Ignatia with the HRT (group P1).

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