Comparative Efficiency of Proproten-100 during the Therapy of Patients with Alcoholism in the Stage of Therapeutic Remission

N. A. Bokhan, A. F. Abolonin, E. N. Krylov, T. P. Vetlugina, S. A. Ivanova, and O. I. Epstein

An open comparative clinical study evaluated the efficiency of Proproten-100 in reliving affective, somatovegetative, behavioral, and cognitive post-withdrawal disorders and manifestations of primary pathological alcohol addiction in patients with alcohol dependence in the stage of therapeutic remission. We compared the efficiency of Proproten-100 and standard symptomatic drugs. The preparation possessed anxiolytic, antidepressant, and vegetostabilizing properties, produced a moderate soporific effect, and had no sedative activity in patients with dysphoric depressions and psychopathic disorders. Proproten-100 was more effective during the therapy of patients with anxious and wistful depressions. Proproten-100 increased the contents of IgG and natural antibodies against S100 protein in the blood from patients. The preparation did not cause side effect or development of tolerance. Proproten-100 has psychotropic properties and holds much promise for long-term treatment of patients with alcohol dependence to reduce the incidence of recurrences.

Key Words: *alcohol dependence; Proproten-100; antidepressant activity; anxiolytic activity; antibodies against S100 protein*

The problem of drug addiction attracts much attention of physicians. Alcoholism is one of the most common addictive disorders. The approaches to intensive therapy of abstinent patients were elaborated. The search for new methods and principles for efficient medicinal rehabilitation of post-withdrawal patients with alcohol dependence (AD) in the initial stage of therapeutic remission is an urgent problem of narcology. Successful therapy of patients with the alcohol withdrawal syndrome (AWS) is not necessarily followed by stable therapeutic remissions. In the stage of remission pathological alcohol addiction is cyclically manifested in affective, insomniac, and somatovegetative disorders, which promotes recurrences of the disease.

Complex studies of new methods for medicinal treatment of post-withdrawal patients and maintenance therapy in remission have considerable theoretical and practical importance. It suggests evaluation of anticraving, thymoanaleptic, anxiolytic, normothymic, cerebroprotective, and other psychotropic properties of medicinal preparations. A new potentiated pharmacological preparation Proproten-100 containing antibodies against brain-specific S100 protein (PAB-S100) and synthesized at the "Materia Medica Holding" Research-and-Production Company produces a variety of psychotropic effects [7,8]. Previous experiments showed that PAB-S100 suppress activity of neurons in the hippocampus and hypothalamus and, therefore, reduce motivational strain realized via these cells and directed toward performing stereotyped alcoholic behavior [6, 7]. Treatment with PAB-S100 should affect the mechanisms of pathological alcohol addiction and duration and quality of remission.

Functionally, S100 proteins are involved in local synaptic activity of neurons in the hippocampus and hypothalamus that play a role in the pathogenesis of AD and AWS [6-8]. Affective and vegetative symptoms associated with dysfunction of these structures during alcohol withdrawal are resistant to therapy. Studies of the severity and dynamics of pathological alcohol addiction during treatment with Proproten-100 are an urgent problem.

Previous clinical observations indicate that Proproten-100 possesses psychotropic and vegetostabilizing properties during the therapy of patients with AWS [1,2,4].

Institute of Mental Health, Tomsk Research Center, Siberian Division of the Russian Academy of Medical Sciences

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Here we studied the efficiency of Proproten-100 during treatment of post-withdrawal patients with AD in therapeutic remission. We compared changes in clinical signs of the post-withdrawal syndrome and somatovegetative, affective, behavioral, and insomniac manifestations of primary pathological alcohol addiction in patients receiving Proproten-100 and standard drugs. The severity of anxious and depressive disorders in these patients was estimated by the Hamilton's scale for anxiety and depression. Immunological parameters were evaluated in laboratory tests.

MATERIALS AND METHODS

We examined 115 patients with stage II AD (110 men and 5 women, average age 40.2±8.43 years). The patients older than 55 years and having internal diseases, epilepsy, decompensated psychopathy, and severe comorbid somatic and neurological disorders were excluded from observations.

The reference group included 45 patients with stage II AD and was randomized by the sex, age, and major clinical and anamnestic characteristics (Table 1).

Patients of the main group (n=70) sublingually received Proproten-100 in a daily dose of 5-8 tablets for 2 weeks. Then the preparation in dose of 1 tablet was given 4-6 times a day. If required, the patients with paroxysmal alcohol addiction received 3 additional tablets of Proproten-100.

Patients of the reference group (n=45) received standard therapy, which included amitriptyline, Neuleptil, piracetam, Pyrroxan, and Grandaxin in daily doses of up to 100, 30, 800, 60, and 100 mg, respectively.

The main average characteristics of AD did not differ in patients of the main and reference groups (Table 2). In patients receiving Proproten-100 the average age for regular alcohol consumption, development of severe AWS, and dipsomania and maximum daily dose of alcoholic beverages slightly surpassed those in patients of the reference group. The average duration of drinking bouts and maximum single dose of alcoholic beverages (vodka) were slightly higher in patients of the reference group.

Examination of patients continued until stable reduction of post-withdrawal symptoms and primary pathological alcohol addiction.

TABLE 1. Age and Microsocial Characteristics of Patients (%)

Parameter		Reference group (n=45)	Proproten-100 (n=70)
Men		95	96
Women		5	4
Age, years		39.80±9.38	40.40±7.88
Education	higher	21	33
	incomplete higher	0	3
	secondary vocational	49	49
	secondary	20	14
	incomplete secondary	10	1
Occupation	employed	88	89
	temporally unemployed	12	11

TABLE 2. Main Clinical and Dynamic Characteristics of Alcohol Dependence in Examined Patients

Parameter		Reference group (n=45)	Proproten-100 (n=70)
Age	first alcohol consumption	16.09±2.36	16.02±1.79
	start of regular alcohol consumption	22.00±4.57	24.04±4.90
	appearance of alcohol-induced amnesia	30.39±6.82	30.97±7.03
	transformation of drunkenness	30.76	30.41±10.22
	development of severe AWS	30.02±6.36	31.15±6.33
	drinking bouts	31.70±7.03	32.70±6.34
	achievement of maximum tolerance	32.3±7.1	32.05±6.29
Duration of drinking bout, days		9.25±8.70	7.05±6.96
Maximum	single dose	271.62±131.81	245.00±109.41
	daily dose	1066.27±427.57	1216.66±646.11

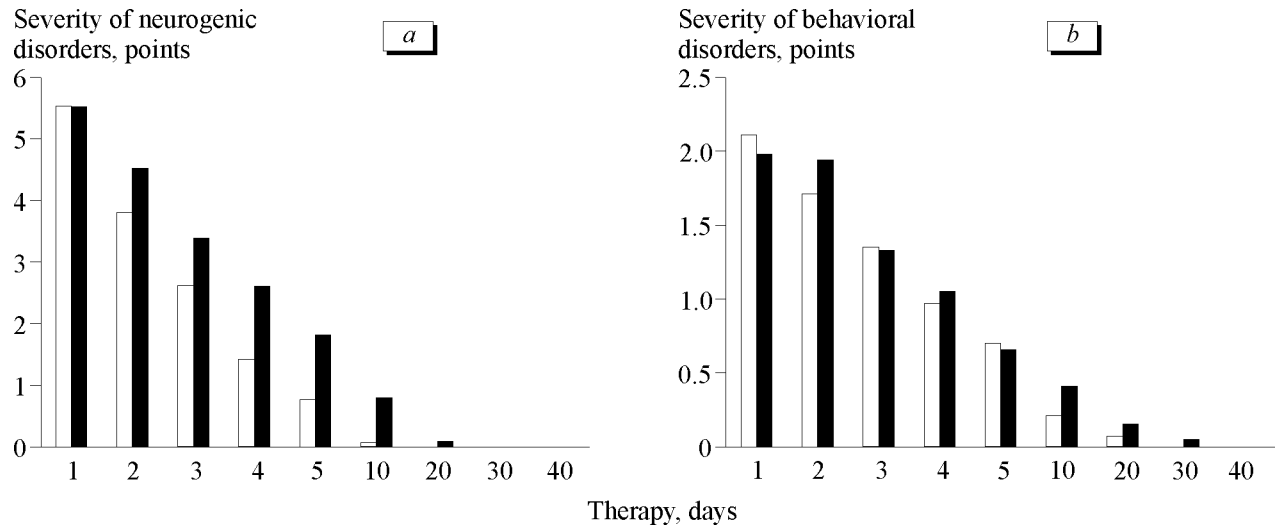

Fig. 1. Dynamics of neurovegetative (*a*) and behavioral disorders (*b*). Light bars: Proproten-100. Dark bars: reference group.

Immunological tests were performed before and after treatment. The concentrations of IgM, IgG, and IgA in the serum were measured by the Manchini's method of radial immune diffusion in agar gel [3,5]. The content of antibodies against brain-specific S100 protein in the serum was estimated by enzyme immunoassay at the Sibmedpribor Company (Novosibirsk).

For standardization we used the unified medical history of patients. The results were analyzed by Student's *t* test and Student's ratio test. The differences were significant at p=0.05.

RESULTS

Initially the severity of AD symptoms was similar in patients of the main and reference groups (Table 3). Neurovegetative, insomniac, and affective disorders were common symptoms in the post-withdrawal period. Neurotic and psychopathic disturbances and manifestations of primary pathological alcohol addiction were rarely observed.

Post-withdrawal symptoms were reduced in a different manner. The average severity of neurovegetative, insomniac, affective, and cognitive disorders and primary pathological alcohol addiction differed in patients of the main and reference groups.

TABLE 3. Initial Severity of Post-withdrawal Symptoms ($M \pm m$, points)

Symptomocomplex	Reference group	Proproten-100
Neurovegetative	5.52±3.43	5.53±2.84
Affective	1.94±0.91	2.21±0.77
Behavioral	1.65±0.76	1.70±0.63
Insomniac	3.55±2.65	4.27±1.89
Alcohol addiction	1.33±0.80	1.60±0.75

On day 5 of therapy neurovegetative disorders were completely reduced in 47 and 28% patients receiving Proproten-100 and standard drugs, respectively (Fig. 1, *a*). On day 10 these differences were less significant.

The severity of behavioral disorders decreased on day 3 of therapy (Fig. 1, *b*). In this period clinical signs were completely reduced in 25 and 14% patients receiving Proproten-100 and standard drugs, respectively. On day 5 these parameters reached 78 and 26%, respectively. Proproten-100 and standard drugs were equally potent in relieving behavioral disorders. Primary pathological alcohol addiction underwent similar changes (Fig. 2, *a*). The degree of alcohol addiction differed from the initial value on day 2 of treatment.

Insomniac disorders were primarily presented by presomnic disturbances (difficulties in falling asleep, 77% patients). Intrasomnic and postsomnic disturbances were rarely observed. The severity of presomnic disturbances differed in patients of the main and reference groups on days 2 and 3 of therapy (Fig. 2, *b*). Changes in the severity of intrasomnic and postsomnic disturbances were similar in patients receiving Proproten-100 and standard drugs (Fig. 2, *c*, *d*). Therefore, Proproten-100 produces the soporific effect, improves cyclic organization of sleep, and recovers quantitative (temporal) and qualitative characteristics of stage I-II slow sleep.

The severity of affective disorders underwent different changes. The total severity of anxious and depressive disturbances in patients of both groups decreased on day 2 of therapy (Hamilton's scale). However, the severity of anxiety and depression differed in patients receiving Proproten-100 and standard drugs (Fig. 2, *e*, *f*). Therefore, Proproten-100 possessed greater antianxiety and antidepressant activities than Grandaxin and amitriptyline.

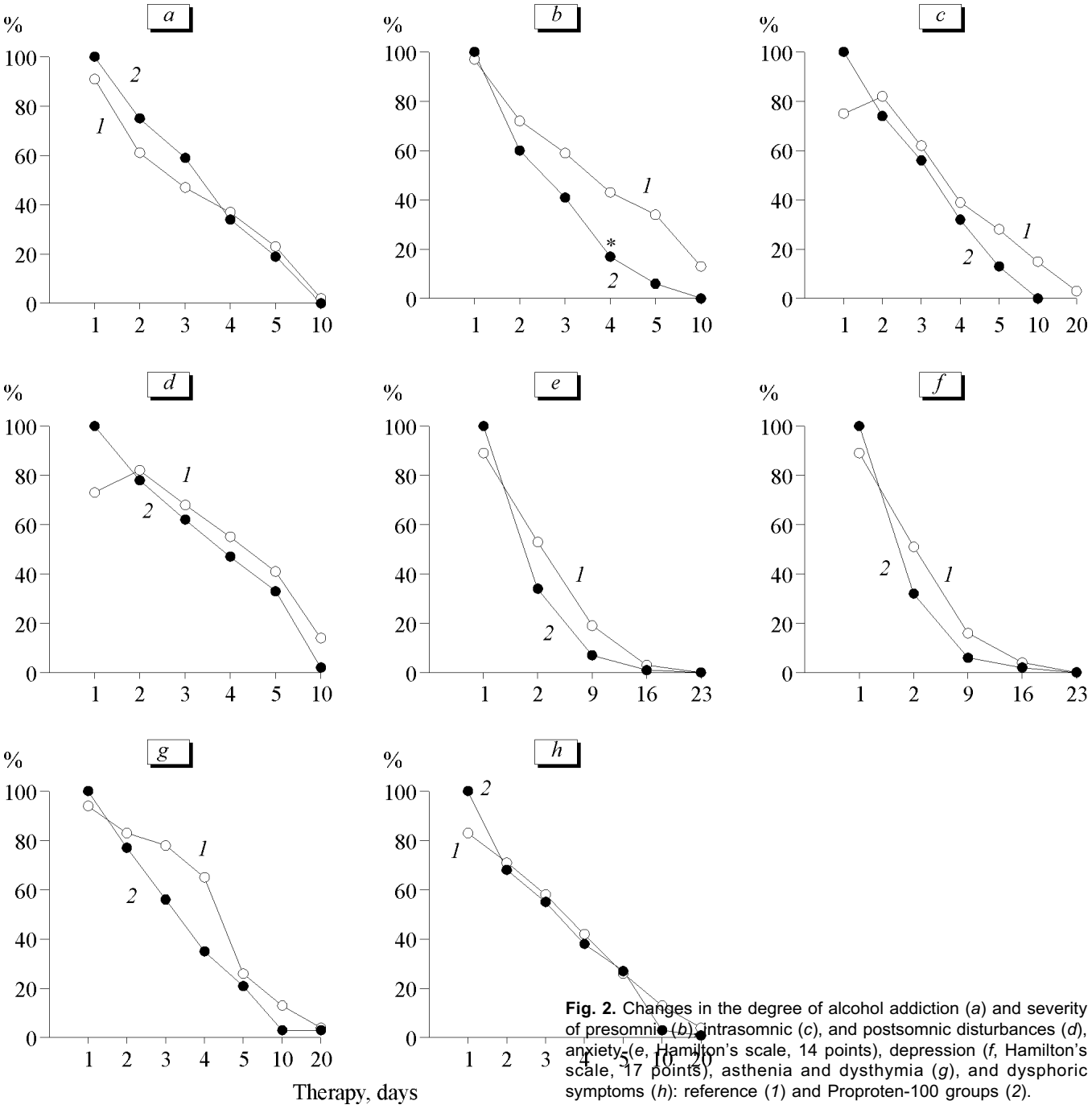

Fig. 2. Changes in the degree of alcohol addiction (*a*) and severity of presomnic (*b*), intrasomnic (*c*), and postsomnic disturbances (*d*), anxiety (*e*, Hamilton's scale, 14 points), depression (*f*, Hamilton's scale, 17 points), asthenia and dysthymia (*g*), and dysphoric symptoms (*h*): reference (*1*) and Proproten-100 groups (*2*).

TABLE 4. Changes in Parameters of Humoral Immunity in Patients with AD (*M*±*m*)

Immune parameters	Before therapy		After therapy	
	reference group	Proproten-100	reference group	Proproten-100
IgM, g/liter	1.18±0.11	1.57±0.13	1.16±0.10	1.51±0.13
IgG, g/liter	12.79±0.99	12.13±0.59	14.96±0.93	14.86±0.92*
IgA, g/liter	2.51±0.18	2.32±0.14	2.80±0.26	2.20±0.18
Antibodies against S100	1.32±0.08	1.28±0.09	1.50±0.13	1.68±0.20*

Note. *$p<0.05$.

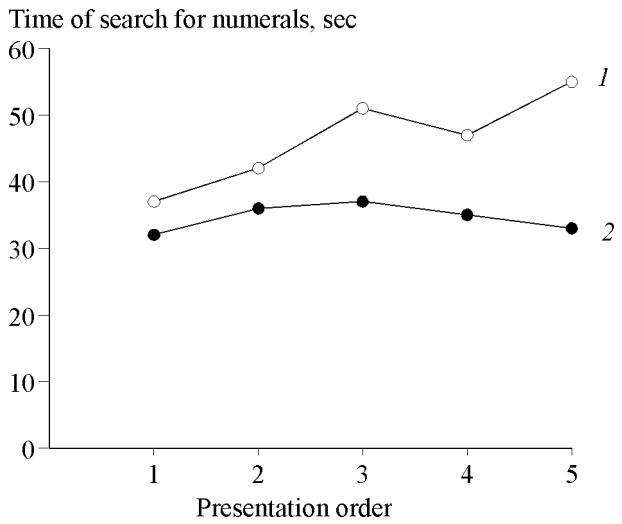

Fig. 3. Study of attention by Schulte's tables: before (*1*) and after therapy (*2*).

The severity of asthenia and dysthymia decreased in patients of the Proproten-100 group on days 3 and 4 of therapy. Then these parameters did not differ between patients of both groups (Fig. 2, *g*).

Proproten-100 and standard drugs similarly relieved dysphoric disturbances (Fig. 2, *h*).

Tests of Schulte and Raven were used to estimate the severity of cognitive disorders. Studies of attention disorders showed that after Proproten-100 therapy the time for task performance decreased by 2.10±0.13 sec, which corresponded to improvement of parameters in the Schulte's test (Fig. 3).

The patients receiving Proproten-100 could perform a seventh-level task the Raven's test (third-level task before therapy). The average time for test performance before and after therapy was 14.02±4.30 and 10.38±2.60, respectively. These data indicate that Proproten-100 improved associative processes, but had no effect on analytic activity of the brain.

The results of clinical examination corresponded to the subjective evaluation of patients. The efficiency of Proproten-100 was considered to be high and intermediate in 43 and 31% patients, respectively. Proproten-100 did not cause side effects.

Before therapy cellular immunity was suppressed in AD patients of both groups. In these patients the contents of Cl3+ and CD4+ lymphocytes were below the control. Standard drugs and Proproten-100 had no effect on cellular immunity in patients.

Studies of humoral immunity in patients of both groups showed that Proproten-100 increases the content of natural antibodies against S100 protein and IgG level, which serves as a favorable prognostic criterion.

Our results show that Proproten-100 is as potent as standard psychotropic preparations amitriptyline, Neuleptil, Nootropil, and Grandaxin in producing the antianxiety, antidepressant, hypnotic, and neuroprotective effects during treatment of AD patients with post-withdrawal disorders. Antidepressant activity of Proproten-100 was higher when the elementary affect primarily included anxious, wistful, asthenic, and asthenodysthymic symptoms. The preparation did not cause side effects and had no sedative activity. Treatment with Proproten-100 was not followed by the development of tolerance. Proproten-100 holds much promise for long-term maintenance therapy of patients with AD in therapeutic remission to reduce the incidence of recurrences.

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