Psychotropic Activity of the Antialcohol Preparation Proproten-100

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Antidepressant Activity of Proproten-100 (antibodies to brain-specific S100 protein in ultralow doses) in patients with stage II alcohol dependence and alcohol withdrawal syndrome was studied in an open comparative clinical trial. The tricyclic antidepressant amitriptyline and benzodiazepine tranquilizer phenazepam served as reference preparations. Anxiolytic activity of Proproten-100 was highly competitive with that of phenazepam. Proproten-100 produced a stronger thymoleptic effect than amitriptyline. The preparation possessed activating properties, affected alcohol addiction, and did not cause side effects. Proproten-100 should undergo clinical tests during the therapy of neurotic, neurosis-like, and subdepressive borderline disorders.

Keywords: *alcohol withdrawal syndrome; Proproten-100; antidepressant activity; anxiolytic activity*

Alcohol dependence (AD) is often accompanied by various psychopathological disorders, including affective, psychopathic, and neurosis-like disturbances. It was hypothesized that alcoholism and psychopathological diseases have common etiological and pathogenetic mechanisms. Therefore, these disorders may be interrelated [16,17,20]. AD is most often accompanied by depressions. Observations performed in Russia and other countries indicate that the incidence of depressive disorders in patients with AD varies from 26 to 60% [6,14,20,21]. Moreover, 95% patients with the alcohol withdrawal syndrome (AWS) suffer form these disturbances [6,11,12,14]. AD-associated depressions differ from endogenous depressions in polymorphism and heterogeneity of the primary affect. These depressions are dissociative and disharmonic. Their severity is high. Clinical signs of these disorders are not characterized by the diurnal rhythm of mood variations and vitality of affective manifestations. Depressive delusions (self-accusation, self-effacement, and retrospective reassessment of past events) are primarily devoted to the alcohol-associated fable [16,17]. Depending on the type of primary affects, AD-associated depressions are divided into anxious, anxious-wistful, wistful, asthenoadynamic, and dysphoric disorders [6, 14]. The duration of AD-associated depression rarely surpasses the minimal duration of endogenous depression (2 weeks) [16,17].

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Psychopathological disturbances in patients with AWS are closely related to sleep disorders, pathological alcohol addiction, and somatovegetative symptoms. Affective disorders are primarily manifested in depressive and anxious symptoms (94%). The directionality of reverse changes in AWS symptoms, including psychopathological signs, is similar. However, the rate of reduction is different and does not directly depend on the initial severity of symptoms [3,11].

Disintoxication and general health-improving therapy relieves psychopathological symptoms of AWS. Psychotropic preparations have anxiolytic, antidepressant, sedative, hypnagogic, and vegetostabilizing properties. Recent studies indicate that benzodiazepine tranquilizers possess anxiolytic and hypnagogic activity. "Long-living" benzodiazepines diazepam and phenazepam with half-elimination periods of 50 and 60 h, respectively, are most potent [1,4]. These preparations produce a strong anxiolytic effect, rapidly reduce serious pre- and intrasomnic disorders, and recover cyclic organization and structure of nocturnal sleep [9,10]. However, benzodiazepine therapy aggravates muscle relaxation and cognitive disorders and impairs attention and operative capacity in AD patients with AWS. The disadvantage of benzodiazepines is rapid development of tolerance [1,4,14].

Neuroleptics (*e.g.*, phenolthiazine derivatives) with pronounced antisecretory activity are contraindicated for patients with AWS due to their relaxant action on the cardiovascular system and general toxic effects [1,14].

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The tricyclic antidepressant amitriptyline possessing not only thymoleptic, but also sedative, anxiolytic, and hypnagogic properties is prescribed for patients with AWS [1,4,7,11,14]. Amitriptyline was proposed as a pathogenetic drug that activates central cholinergic processes in patients with AD. Amitriptyline produces the atropine-like cholinolytic effect, which aggravates the symptoms of AWS and restricts the use of this preparation [6,11,14].

Previous observations revealed heterogeneity of depressive disorders in patients with AD. Various metabolic preparations, including Alcogal, Biotredin, Deltaran, and mexidol, outperform standard antidepressants in the effect on patients with AWS and serious depressive disorders [18].

Proproten-100 is highly efficient during the therapy of patients with AWS. Experimental and clinical observations showed that this preparation possesses psychotropic activity [2,5,8,13,15,16].

Here we compared psychotropic activity of the antialcohol preparation Proproten-100 and standard drugs used to relieve AWS (phenazepam and amitriptyline).

MATERIALS AND METHODS

Proproten-100 [2,5,8], phenazepam, and amitriptyline [11] were tested at basic clinical departments of the Moscow Institute of Psychiatry, Russian State Medical University, and Russian Medical Academy of Postgraduate Education.

We examined 256 patients with stage II AWS that had severe somatovegetative, neurological, and psychopathological symptoms and were hospitalized after alcohol consumption for many days. The patients with associated intercurrent diseases in exacerbation and stage III AD were excluded from observations.

The patients with AWS were examined daily at the same time.

A double-blind, placebo-controlled trial was performed with 172 patients. The patients sublingually received Proproten-100 or placebo in a single dose of 1 tablet at 1-h (first 5 treatments) and 2-3-h intervals. The efficiency of preparations was evaluated after 5-6 h. The patients were divided into respondents and non-respondents. Non-respondents additionally received standard disintoxication and general health-improving drugs and served as the control. Respondents received Proproten-100 monotherapy.

Amitriptyline in a daily dose of 75 mg was given to 34 patients; 50 patients received phenazepam in a daily dose of 2 mg. These preparations were administered in combination with standard disintoxication drugs.

For standardization we used the individual medical history of patients. The severity of AWS symptoms was determined by a 3-point scale. Between-group differences were estimated by Student's t test and Student's ratio test. The differences were significant at $p \leq 0.05$.

RESULTS

The main anamnestic and age characteristics did not differ in examined patients (Table 1). The patients receiving Proproten-100 were slightly older than other patients. In phenazepam-treated patients the last drinking bout was longer than in other patients. During the last drinking bout most patients consumed alcoholic beverages in intermediate and high daily doses.

The patients were divided into respondents (n=87) and non-respondents (n=85) 5-6 after the start of a placebo-controlled trial with Proproten-100 and placebo. We revealed that all respondents received Pro-

TABLE 1. Age, Anamnestic Characteristics, and Average Duration of Psychopathological and Somatovegetative Disorders in Patients with AWS ($M \pm m$)

Parameter	Placebo (control, n=85)	Proproten-100 (n=87)	Amitriptyline (n=34)	Phenazepam (n=50)
Age, years	41.80±1.11	43.50±1.12	39.20±1.62	42.00±1.19
Duration of disease, years	13.70±0.87	13.50±0.70	12.5±1.0	14.00±0.70
Duration, days				
last drinking bout	8.60±0.77	9.60±0.71	10.10±1.09	10.20±0.70
AWS symptoms				
addiction	2.70±0.12	1.90±0.09**	2.00±0.25**	2.10±0.29
anxiety	2.40±0.15	1.90±0.11**	2.50±0.22	1.60±0.09**
depression	3.50±0.17	1.90±0.14*	3.70±0.42	3.60±0.29
sleep disorders	3.20±0.11	2.60±0.13**	3.10±0.35	1.40±0.09*
somatovegetative disorders	3.40±0.13	2.90±0.17**	4.90±0.53	4.10±0.32

Note. *p<0.01 and **p<0.05 compared to the control group.

proten-100. These data indicate that Proproten-100 was efficient during early treatment of patients with AWS.

Alcohol addiction, sleep disorders, psychopathological disturbances, and somatovegetative symptoms associated with affective diseases were rapidly relieved in patients of various groups. Proproten-100, amitriptyline, and phenazepam exhibited selectivity in relation to the main symptoms of AWS (compared to disintoxication and general health-improving drugs, Table 1).

Test preparations more rapidly relieved alcohol addiction than disintoxication drugs. Anxious symptoms were reduced more rapidly in patients receiving phenazepam and Proproten-100. In the Proproten-100 group depressive and somatovegetative disorders disappeared over a short time. Phenazepam rapidly normalized sleep. Proproten-100 produced a similar effect (Table 1). Amitriptyline was low efficient in reliving the symptoms of AWS, which is probably associated with cholinolytic activity of this preparation [7,11].

Our findings show that antidepressant, anxiolytic, anti-craving, and vegetotropic activity of Proproten-100 is highly competitive with that of the benzodiazepine derivative phenazepam. Proproten-100 produces a stronger effect than amitriptyline. Proproten-100 selectively affects depressions differing in the primary affect and relieves alcohol addiction, somatovegetative disturbances, and sleep disorders.

The number of patients with alcohol addiction, anxious and wistful depression, and somatovegetative disturbances significantly decreased in the Proproten-100 and control groups on day 2 of therapy (Fig. 1).

On day 2 the severity of anxious and wistful depression, sleep disorders, and somatovegetative disturbances was different in patients of the Proproten-100 and control groups. Moreover, the degree of asthenoadynamic depression tended to differ between these patients (Fig. 2, *a-e*, *g*). It should be emphasized that Proproten-100 had no effect on manifestations of dysphoria (Fig. 2, *f*).

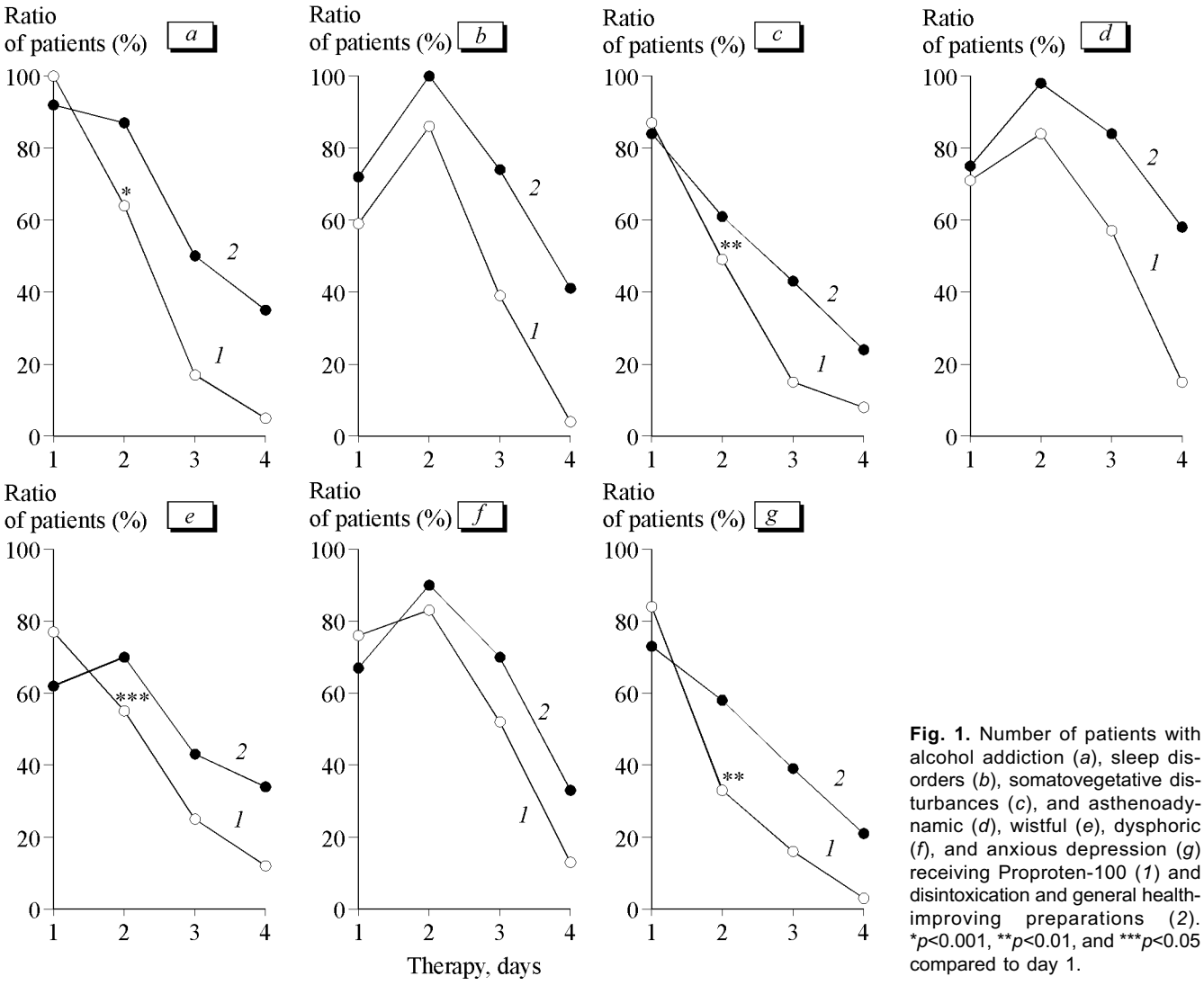

Fig. 1. Number of patients with alcohol addiction (*a*), sleep disorders (*b*), somatovegetative disturbances (*c*), and asthenoadynamic (*d*), wistful (*e*), dysphoric (*f*), and anxious depression (*g*) receiving Proproten-100 (*1*) and disintoxication and general health-improving preparations (*2*). *p<0.001, **p<0.01, and ***p<0.05 compared to day 1.

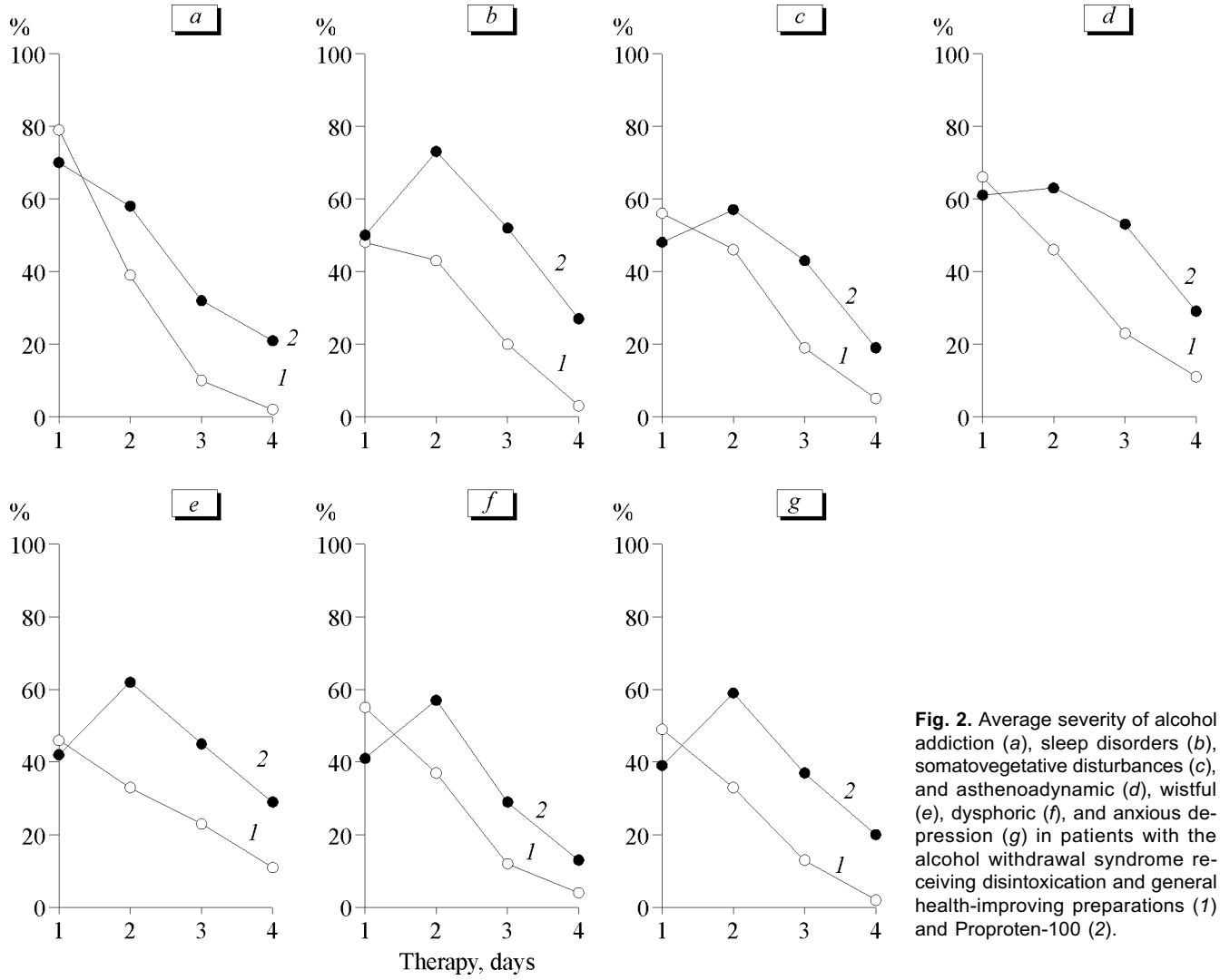

Fig. 2. Average severity of alcohol addiction (*a*), sleep disorders (*b*), somatovegetative disturbances (*c*), and asthenoadynamic (*d*), wistful (*e*), dysphoric (*f*), and anxious depression (*g*) in patients with the alcohol withdrawal syndrome receiving disintoxication and general health-improving preparations (*1*) and Proproten-100 (*2*).

Our results show that Proproten-100 has antidepressant, anxiolytic, re-dynamic, hypnagogic, and vegetostabilizing therapeutic properties. This preparation does not cause the sedative effect. Anxiolytic activity of Proproten-100 is highly competitive with that of the tranquilizer phenazepam. Proproten-100 possesses psychotropic activity. This preparation should undergo clinical tests during the therapy of patients with neurosis-like and depressive disorders.

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