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Efficacy and Safety of Galantamine (reminyl) for Dementia in Patients with Parkinson's Disease (an open controlled trial)

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An open controlled trial of the use of galantamine at a maximum dose of 16 mg/day included 41 patients with Parkinson's disease with dementia randomized to a galantamine treatment group (21 patients) and a control group (20 patients). Cognitive, neuropsychiatric, and motor symptoms were assessed clinically before the trial and at 4, 12, and 24 weeks, using the Mini Mental State Examination (MMSE), the cognitive Alzheimer's Disease Assessment Scale (ADAS-cog), the clock drawing test, the Frontal Assessment Battery (FAB), and the Neuropsychiatric Inventory (NPI) with assessment of distress in relatives. Patients treated with galantamine had better scores on the MMSE ($p < 0.05$), ADAS-cog ($p < 0.05$), the clock drawing test ($p < 0.05$), and the FAB ($p < 0.01$) at the end of the study period as compared with the control group. Changes in total point scores on the NPI-12 at the ends of weeks 12 and 24, as compared with the beginning of the trial, were in favor of the group treated with galantamine, with significant changes in the hallucinations ($p = 0.0002$), anxiety ($p = 0.04$), sleep disturbance ($p = 0.04$), and apathy ($p = 0.006$) sections. Galantamine treatment was accompanied by decreases in the level of distress in patients' relatives ($p = 0.007$) and improvements in daily activity ($p = 0.003$). Improvements in gait and decreases in freezing and falls were seen in the galantamine treatment group. However, two patients of this group showed minor increases in tremor. Side effects (drooling, postural hypotension, nausea, dysuria) occurred in seven patients (30%).

KEY WORDS: Parkinson's disease, dementia, galantamine.

Successes in the current pharmacotherapy of motor disorders in Parkinson's disease (PD) have yielded significant improvements in the duration of life among these patients. However, new questions have arisen in relation to the treatment of this disease, associated primarily with the development of non-motor complications – dementia, psychotic disorders, and affective and behavioral derangements [5, 6, 12]. The development of dementia leads to significant exacerbation of social and daily maladaptation, causes difficulty with patient care, and sharply increases the risk that psychotic disorders will develop during treatment [1, 3, 14].

In Russia, the main responsibility for patient care falls on patients' relatives. Increases in disease severity increase the difficulty of providing care, which in turn initially leads to degradation of the carer's mental state (development of depression, anxiety disorders, sleeplessness, and feelings of isolation and hopelessness) and then results in the onset or exacerbation of chronic somatic illnesses. Questionnaire studies have demonstrated that people responsible for caring for patients visited physicians 46% more frequently and took medications 71% more frequently than people of the same age but without the responsibility of caring for patients with dementia [19]. Furthermore, the development of serious somatic illnesses was more common in spouses caring for patients with more marked impairments to daily activity [33]. It has also been demonstrated that care for severe patients is an independent risk factor for an increased death rate among carers themselves [9]. All these points

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undoubtedly have negative social consequences and produce increases in the economic costs.

The development of cognitive disturbances and dementia in PD results from damage to dopaminergic neurons in the medial part of the substantia nigra [16], to dopaminergic neurons in the ventral tegmentum of the midbrain [24], which form the mesocortical pathway, to adrenergic neurons in the locus ceruleus [41], and to progressive death of cholinergic neurons in the basal nucleus of Meynert and the cerebral cortex [10, 11]. The pathogenesis of the death of cholinergic and other populations of neurons involves excitotoxic mechanisms associated with chronic tonic stimulation of NMDA-glutamate receptors and the subsequent development of secondary hypofunction of the glutamatergic neurotransmitter system. The interaction of the glutamatergic and cholinergic cerebral systems is therefore of particular interest to investigators [38].

In attempts to explain the mechanism by which psychotic disorders arise in PD, the main accent is on the ability of dopaminomimetics to induce excess stimulation of dopamine receptors in the limbic system of the brain [1, 2, 21, 22]. This stimulation of dopamine receptors, particularly on the background of dopamine receptor hypersensitivity, can provoke hallucinations, illusions, and other severe mental disturbances [3, 27]. The neuroleptics, including atypical neuroleptics, are often ineffective, and the main task is to provide safe management of psychotic disorders in dementia. The use of the atypical antipsychotics olanzapine and risperidone for this purpose increased the risk of strokes by a factor of three as compared with a group of patients given placebo [39], while the use of typical neuroleptics (haloperidol, aminazine) can result in the development of severe complications in the form of akinetic crisis, which is lethal in 50–60% of cases [2]. Even when use of antipsychotics eliminates psychotic disturbances, the cost is deterioration of motor functions [17]. Thus, given the unavoidable actions of neuroleptics on dopamine receptors in the striatum, the ideal is to eliminate psychotic derangements without using these agents.

An alternative approach might consist of using cholinomimetics with antipsychotic properties [4, 18]. Reports of positive effects with the cholinesterase inhibitor rivastigmine (Exelon) [13, 31] and Arisept (donepezil) [20] have supported the validity of this approach in PD complicated by dementia. However, some trials have demonstrated increases in motor impairments and deterioration of emotional state on the background of rivastigmine [30] and donepezil [25] treatment. Cholinesterase inhibitors with additional N-cholinomimetic activity, such as galantamine (Reminyl), may have advantages over other agents of this group, as galantamine can prevent the suppression of N-cholinoreceptor expression developing on the background of treatment with cholinesterase inhibitors, facilitating dopamine release in the striatum [7, 42]. It is interesting to note that the extent of the cholinergic deficit in corticolimbic brain structures in PD complicated by dementia is more than twice as great as in Alzheimer's disease [11]. In addition, in PD complicated by dementia, muscarinic postsynaptic receptors are better preserved than in Alzheimer's disease [8, 29]. This therefore leads to the suggestion that cholinergic agents might be more effective in PD-associated dementia than in Alzheimer's disease. To date, the world has produced only one eight-week trial using validated neuropsychological, neuropsychiatric, and motor scales of the use of galantamine (Reminyl) in patients with PD complicated by dementia [7]. No such trials have been conducted in Russia. Thus, we elected to perform a 24-week controlled study of the efficacy and safety of galantamine (Reminyl) treatment in patients with PD-associated dementia.

The aim of the present work was to assess the efficacy, safety, and tolerance of galantamine (Reminyl) treatment in patients in the late stages of PD, complicated by dementia. The study evaluated the effects of treatment on cognitive functions, psychotic, behavioral, and emotional disorders, the ability of the patients to self-care, and the motor manifestations of PD, as well as the level of distress in patient carers.

MATERIALS AND METHODS

The open, controlled trial was performed at the clinics and nervous diseases departments of the Military Medical Academy, St. Petersburg.

Inclusion criteria for patients were: MMSE scores of less than 25; presence of dementia as per ICD-10 criteria developing two years from the onset of PD; consistency of the PD diagnosis with the British Brain Bank criteria; the ability of the patients to perform neuropsychological tests; and the existence of a person constantly providing care for the patient.

Exclusion criteria for patients were: the presence of significant cardiovascular diseases (altered cardiac rhythm), diseases causing bronchial obstruction, signs of hepatic or renal pathology; use of cholinolytics, cholinesterase inhibitor, or nootropes; history of acute cerebrovascular episodes in the six months preceding the trial; presence of marked depression (>18 points on the Hamilton scale), delusions, or neurovisualization signs of focal vascular brain lesions in strategically important zones (thalamus, hippocampus, bilateral lacunae in the globus pallidus), or other organic brain disease.

In accord with the inclusion criteria, all patients (41 patients) were randomly assigned to two groups – an experimental group, in which patients received galantamine in addition to ongoing treatment (21 patients), and a control group (20 patients) who continued ongoing treatment.

Galantamine (Reminyl, Janssen Silag) was given by the following protocol: 4 mg twice daily for the first four weeks, and then 8 mg twice daily to the end of the 24-week trial period. The decision to limit the galantamine dose to

16 mg/day was based on previous studies, which demonstrated the absence of any significant difference in efficacy when the dose was increased to 24 mg/day [36], though the frequency and severity of side effects on using this dose were greater than those seen with the dose of 16 mg/day.

Patients were investigated at the ends of weeks 4, 12, and 24 (second, third, and fourth visits) of treatment or at the same time points in the study period (control patients).

Investigations included the following methods: clinical and neurological examination, measurement of pulse, arterial pressure, and respiratory rate, performance of orthostatic testing, and assessment of motor and cognitive functions; changes in psychotic, behavioral, and emotional disorders were assessed; ECG traces were recorded, and biochemical blood tests were performed before treatment started and then only when indicated. At each physician visit, patients were asked about likely side effects.

The stage of PD was established using the Hoehn and Yahr scale; patients' motor function was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), part III, "motor function."

Criteria for treatment efficacy were evaluated in terms of changes in measures on the Mini Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale (ADAS-cog), the Frontal Assessment Battery (FAB), the clock drawing test [35], the Neuropsychiatric Inventory (NPI-12), and the Disability Assessment for Dementia (DAD) at the end of treatment week 24 as compared with baseline; group differences were also assessed between the control and active treatment groups at the end of the study. The first four scales allowed assessment of the state of and changes in patients' cognitive functions during treatment. Information relating to changes in behavioral, emotional, and psychotic disorders, as well as self-care ability and the ability to perform the activities of daily living, was obtained from the last two of these scales from patients' relatives or persons caring for patients.

The NPI-12 neuropsychiatric questionnaire noted above consisted of 12 subsections including assessment of delirium, hallucinations, excitation/aggression, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/emotional lability, pathological motor activity, sleep disturbances and nocturnal behavior, changes in appetite, and food-related behavior. The severity of each symptom was assessed from "mild" (1 point) through "moderate" (2 points) to "severe" (3 points) and in terms of frequency, from "episodic" (1 point) through "periodic" (2 points) and "frequent" (3 points) to "very frequent" (4 points) . the total points for each subdivision of the questionnaire were used to calculate scores by multiplying severity by frequency. The maximum possible total score was 144.

The neuropsychiatric questionnaire allowed the extent to which a symptom had negative impact on emotional and psychological state of the person caring for the patient to be assessed (on the "distress" subsection). The relative or person caring for the patient evaluated distress on a five-point scale: 0 = no distress, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe distress. The greatest level of distress on all neuropsychological symptoms was 60 points.

Questioning of relatives on the scale assessing disability in patients with dementia determined whether, in the last two weeks, patients had performed particular types of everyday activity without assistance or reminders – including self-care and observation of hygiene habits, dressing (correct selection of clothes in relation to the situation, season, neatness, etc.), using the lavatory, consumption and preparation of food, using a telephone, going out of the house and from one place to another, organizing finances, knowing when to take medications, do housework, taking an interest in organizing rest time, being able to find the way home independently without breaking safety rules, etc. The greater the points score on this scale, the more adapted to performing daily tasks the patient was considered to be. The maximum score was 40 (at which patients had no difficulty in performing daily tasks).

Patients underwent magnetic resonance tomography of the brain, using a Magnetom Vision system from Siemens with a magnetic field of 1.5 T in the T1- and T2-weighted and FLAIR/STIR regimes.

The safety and tolerance of the agent was assessed by biochemical blood tests for ALT, AST, AlkP, and creatinine, along with ECG recordings, monitoring of side effects, and assessment of motor functions on subdivision II of the UPDRS scale.

Results were analyzed statistically using a personal computer running Statistica for Windows 6.0. Significant differences between groups at repeat visits during the trial, as well as in comparison with baseline, were identified using dispersion analysis of repeat measurements using non-parametric tests (the Kruskal–Wallis test and the Wilcoxon ranked paired comparisons test (W) with the Bonferroni correction). Analysis included all patients who performed the therapeutic-diagnostic measures at all visits.

Two patients dropped out early from the control group because of the inability to perform the neuropsychological tests for mental state. All 21 patients in the experimental group and 18 in the control group completed the study.

Mean ages, gender composition, durations of PD and dementia, severity of parkinsonism, mean dose of L-DOPA agents, and levels of education were not significantly different in the experimental and control groups (Table 1).

Most patients (21, i.e., 51.2%) had stage 3 PD; 16 (39.1%) had stage 4 and four (97%) had stage 2.5. Dementia in all patients appeared at least five years from the onset of PD. The mean points scores on the MMSE, ADAS-cog, and FAB were not significantly different between the two groups. Most patients (28, i.e., 68.3%) were diagnosed with moderate dementia. The remaining 13 patients had mild dementia.

TABLE 1. Clinical and Clinical-Neuropsychological Measures Characterizing Patients in the Trial

Measure	Experimental group (n = 21)	Control group (n = 20)
Age, years	68.6 ± 9.3	72.6 ± 8.6
Duration of PD, years	8.9 ± 2.2	9.3 ± 2.5
Duration of dementia, years	1.3 ± 0.7	1.0 ± 0.4
Education, years	11.2 ± 0.8	10.6 ± 0.7
Stage of PD	3.2 ± 0.5	3.3 ± 0.6
UPDRS part III, points	35.4 ± 11.8	37.2 ± 14.3
MMSE, points	17.6 ± 3.3	18.1 ± 3.6
ADAS-cog, points	23.5 ± 1.2	22.9 ± 1.5
Frontal Assessment Battery, points	7.2 ± 1.4	7.8 ± 1.4
L-DOPA dose, mg	785.8 ± 119.3	728.2 ± 125.3
Number of patients treated with:		
dopamine receptor agonists	14	12
neuroleptics	4	5
other psychotropic agents	21	20

Psychotic disorders consisted of illusions, hallucinations, and delusions. All patients described histories of visual hallucinations; at the moment of recruitment into the study, 31 patients (75.6%) were experiencing these. Of these, 14 patients experienced combined visual-auditory hallucinations and 19 had hallucinations preceded by visual illusions. Delusional perceptions were present in seven patients. The period from the appearance of the first psychotic disturbances was 6–48 months. The frequency of hallucinations was less than once a week in five patients, about once a week in nine, several times a week in seven, and daily in 10 patients. The most frequent mental disturbances in patients were hallucinations (75.6%), irritability (63.4%), apathy (56.1%), depression (51.2%), anxiety (34.1%), and excitability/aggression (34.1%). The rarest were euphoria (2.4%) and disturbances to food-related behavior (21.9%). Nocturnal sleep disturbances and daytime drowsiness occurred in all patients.

The greatest level of distress in patients' relatives was caused by hallucinations, delusions, aggression, and irritability. It should be noted that moderately severe distress was experienced by more than half (56%) of the relatives, and 80% reported that the patient's mental state elicited at least moderate distress.

All patients received L-DOPA agents. Combined treatment with dopamine receptor agonists was used in 14 patients (67%) in the experimental group and 12 (60%) in the control group. The duration of this treatment was 6–18 years. Of all patients included in the study, 21.9% received neuroleptics in relation to psychotic and behavioral disorders, 12.1% were taking antidepressants, 46.3% took anxiolytics, and 97.5% used sleeping medications. About half the patients received more than one psychotropic medication.

Medication was reviewed after four weeks, and antiparkinsonism and other psychotropic agents were withdrawn or added as required. All changes in treatment were recorded and analyzed at the end of the study.

RESULTS AND DISCUSSION

Treatment with galantamine had positive effects on cognitive impairments on the MMSE and ADAS-cog scales as compared with baseline and the control group. Significant changes were seen at the ends of weeks 12 and 24 of the trial (Table 2). The control group showed a clear tendency to progression of cognitive disorders by the end of the observation period.

Analysis of the dynamics of changes in particular cognitive functions in patients treated with galantamine showed that the most significant changes by the ends of study weeks 12 and 24 were in measures such as attention (MMSE serial counting subdivision, $p = 0.004$), word remembering (ADAS-cog scale, $p = 0.004$), speech activity (controlled verbal associations, $p = 0.02$), tests for following conflicting instructions and sequencing actions and intervals (Frontal Assessment Battery, $p = 0.001$), and visual-spatial function (the clock drawing test, $p = 0.03$). It should be noted that significant changes on the Frontal Assessment Battery were obtained by the end of four weeks of treatment with galantamine at a dose of 8 mg/day, which provides evidence for the significant role of the

TABLE 2. Changes in Measures of Severity of Cognitive Impairment during Treatment

Measure	Before treatment	Week 4	Week 12	Week 24
MMSE				
experimental group	17.6 ± 3.3	19.1 ± 1.9	21.8 ± 1.3*	21.3 ± 1.9*#
control group	18.1 ± 3.6	19.3 ± 1.6	18.6 ± 1.4	16.8 ± 1.4
ADAS-cog				
experimental group	23.5 ± 3.8	23.0 ± 2.8	21.3 ± 2.7*#	20.2 ± 2.2*#
control group	22.9 ± 2.9	22.1 ± 2.7	25.7 ± 2.1	25.9 ± 2.6
Frontal Assessment Battery				
experimental group	7.2 ± 1.4	8.7 ± 1.6*#	9.1 ± 1.1*#	9.7 ± 1.5**##
control group	7.8 ± 1.3	7.9 ± 1.8	7.5 ± 1.7	7.1 ± 1.2
Clock drawing test				
experimental group	3.8 ± 1.5	4.7 ± 1.7	5.1 ± 1.9*	4.7 ± 1.5*#
control group	4.3 ± 1.5	4.7 ± 1.6	4.2 ± 1.5	4.0 ± 1.6

Notes. Significant differences compared with baseline: *$p < 0.05$; **$p < 0.01$; significant differences compared with control group: #$p < 0.05$; ##$p < 0.01$.

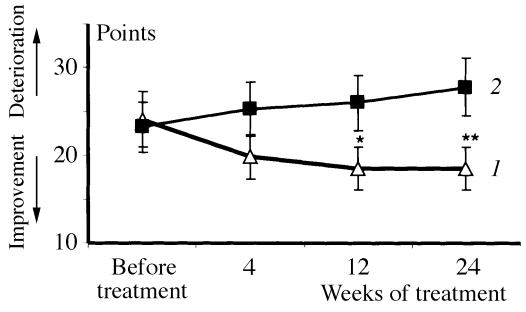

Fig. 1. Severity of psychotic and behavioral disturbances in the experimental (curve *1*) and control (curve *2*) groups of patients, neuropsychiatric questionnaire, at different stages of treatment. Significant differences compared with control group: *$p = 0.02$; **$p = 0.005$.

cholinergic deficit in producing frontal lobe dysfunction in PD-associated dementia and that the agent has a quite rapid onset of effect.

Our results are consistent with data obtained by other investigators [32] assessing metabolism and brain perfusion using positron emission and single-photon computerized tomography. After the therapeutic effect was obtained, these authors noted significant improvements in glucose metabolism and cerebral perfusion in the frontal lobes and cingulate gyrus, which correlated with improvements in the performance of tests for frontal dysfunction. Given that disorders of executive (frontal) and visual-spatial functions, as well as attention deficiency, are the leading cognitive defects in PD, the ability of cholinergic treatment to compensate for these impairments is of undoubted interest.

The dynamics of psychotic, behavioral, and affective disorders on the neuropsychiatric questionnaire also reflected the efficacy of galantamine (Table 3). The total points scores in this group showed a statistically significant decrease as compared with baseline by 12 weeks (–4.6 points, $p = 0.03$) and 24 weeks (–4.7 points, $p = 0.009$) of the study, as well as in comparison with the control group at visits at these times (–4.1 points, $p = 0.02$; –7.8 points, $p = 0.005$, respectively) (Fig. 1). The most marked positive changes occurred in relation to hallucinations. By the end of treatment week 4, there was an almost two-fold reduction in the severity of hallucinations, and by the end of weeks 12 and 24 the mean points scores for this symptom decreased by factors of 3.7 (from 4.1 to 1.1 points, $p = 0.0002$). The mean hallucinations score in the control group was slightly lower (3.8 ± 1.7) than in the experimental group (4.1 ± 1.2), but increased significantly by the end of the study, to 4.9 ± 1.5 ($p = 0.044$), when the intergroup difference at the end of the trial was by a factor of more than four, in favor of patients treated with Reminyl. It was therefore of interest to note the trial results reported by Ballard et al. [8], who demonstrated significant reductions in the cholinergic marker choline acetyltransferase in the occipital associative cortex in patients with visual hallucinations as compared with patients without hallucinations. Decreases in the severity of visual hallucinations correlating with improvements in cerebral perfusion in the occipital lobes were seen using single-photon computerized tomography [26, 34]. Some investigators believe that frontal lobe dysfunction can also make a contribution to the development of hallucinations in patients with PD, even at the stage of moderate cognitive impairments not reaching the level of dementia [23]. It should also be noted that the

TABLE 3. Changes in Mental Disturbances in the Experimental Group, Neuropsychiatric Questionnaire (NPI/12), $M \pm SD$

Symptom	Before treatment	Treatment weeks		
		4	12	24
Delusions	1.5 ± 0.6	1.1 ± 0.3	1.4 ± 0.6	1.2 ± 0.4
	1.1 ± 0.4	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.3
Hallucinations	4.1 ± 1.2	2.2 ± 0.7*#	1.1 ± 0.5**##	1.1 ± 0.5**##
	3.8 ± 1.7	3.9 ± 1.2	4.2 ± 1.2	4.9 ± 1.5*
Aggression	1.8 ± 0.5	1.5 ± 0.5	1.4 ± 0.7	1.5 ± 0.9
	2.0 ± 0.6	2.1 ± 1.1	2.1 ± 0.9	1.8 ± 1.2
Depression	2.5 ± 0.5	2.4 ± 0.5	2.6 ± 0.7	2.5 ± 1.1
	2.3 ± 0.5	2.5 ± 0.9	2.6 ± 1.1	2.9 ± 1.2
Anxiety	1.8 ± 0.4	1.7 ± 0.5	1.2 ± 0.5*	1.4 ± 0.5*##
	2.0 ± 0.7	2.2 ± 0.7	2.4 ± 0.9	2.3 ± 0.5
Euphoria	0.4 ± 0.1	0.4 ± 0.1	1.3 ± 0.3	0.8 ± 0.2
	0.1 ± 0.05	0.3 ± 0.04	0.5 ± 0.1	0.4 ± 0.3
Apathy	3.5 ± 0.9	3.3 ± 1.1	2.1 ± 0.5*	2.1 ± 0.3*##
	3.6 ± 1.1	3.9 ± 1.0	3.8 ± 1.5	4.1 ± 1.1
Irritability	2.2 ± 0.7	2.1 ± 0.5	2.1 ± 0.3	2.4 ± 0.5
	1.9 ± 0.4	2.2 ± 1.1	1.8 ± 0.5	1.9 ± 0.3
Disinhibition	0.8 ± 0.2	0.7 ± 0.1	1.0 ± 0.3	0.9 ± 0.2
	1.1 ± 0.2	1.5 ± 0.3	1.3 ± 0.2	1.2 ± 0.5
Pathological motor activity	0.7 ± 0.2	0.5 ± 0.1	0.7 ± 0.3	0.6 ± 0.2
	1.0 ± 0.3	0.7 ± 0.2	0.9 ± 0.3	0.8 ± 0.2
Sleep	2.1 ± 0.7	1.2 ± 0.5	1.1 ± 0.2*	1.1 ± 0.2**
	1.8 ± 0.5	1.6 ± 0.5	1.9 ± 0.3	2.2 ± 0.5
Impaired food-related behavior	1.7 ± 0.3	1.7 ± 0.5	1.5 ± 0.2	2.0 ± 0.7
	1.5 ± 0.5	2.1 ± 0.9	2.2 ± 0.5	2.0 ± 0.3
Total points	23.1 ± 1.5	18.8 ± 1.8	18.5 ± 1.3*#	18.4 ± 1.1**##
	22.2 ± 1.1	23.3 ± 1.5	24.6 ± 1.8	26.2 ± 1.9

Notes. Significant differences compared with baseline: $^{*}p < 0.05$; $^{**}p < 0.01$; significant differences between Reminyl-treated experimental group and control group at study point: $^{\#}p < 0.05$; $^{\#\#}p < 0.01$.

effects of Reminyl on both cognitive functions and the activities of daily living were greater in patients with hallucinations (16 patients) as compared with the five patients without hallucinations at recruitment into the trial. The mean change on the Frontal Assessment Battery at the end of the study in patients with hallucinations was +2.9 points, compared with +1.6 points in patients without hallucinations ($p = 0.03$); on the clock drawing test, the mean changes were by +1.8 and +0.6 points in these groups respectively ($p = 0.048$); on the DAD scale, mean changes were by +2.1 and +0.8 points. It is clear that the presence of hallucinations is evidence of marked cholinergic cerebral deficit and may serve as a predictor for positive responses to treatment with cholinesterase inhibitors.

Significant influences on other impairments in dementia were obtained for anxiety ($p = 0.04$), apathy ($p = 0.006$), and sleep disturbance, with a reduction in daytime drowsiness and improvement in night-time sleep ($p = 0.044$).

Thus, use of Reminyl produced significant decreases in the severity of psychotic, behavioral, and emotional impairments in patients with PD-associated dementia.

Given that these are the symptoms which evoked the greatest levels of distress in patients' relatives, there was a consistent reduction in their negative influences on the emotional state of carers (Fig. 2). By the ends of weeks 12 and 24, the severity of distress in the relatives of patients treated with Reminyl was significantly lower than baseline and in the control group ($p = 0.03$ and $p = 0.007$, respectively).

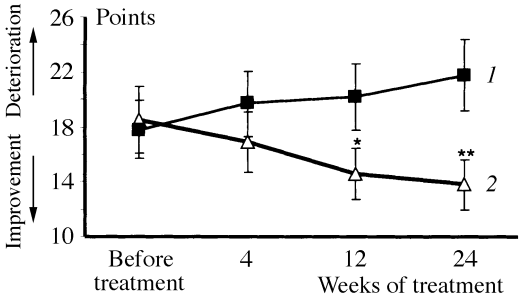

Fig. 2. Severity of distress in relatives of patients in the experimental (curve *1*) and control (curve *2*) groups of patients at different stages in the trial, neuropsychiatric questionnaire. Significant differences compared with control group: $*p = 0.03$; $**p = 0.007$.

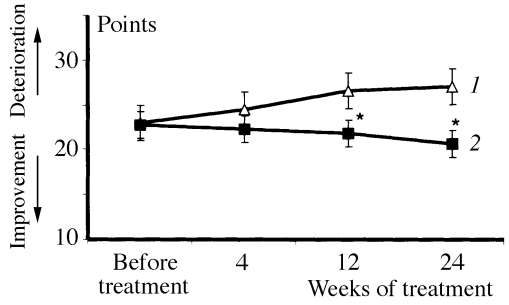

Fig. 3. Disability Assessment for Dementia scores in the experimental (curve *1*) and control (curve *2*) groups at different stage of the trial. Significant differences compared with control group: $*p = 0.003$.

Improvements in patients' cognitive functions and mental state were accompanied by changes in the ability to perform the activities of daily living and adaptation to circumstances (Fig. 3). Use of the DAD scale showed that at 12 and 24 weeks there were statistically significant ($p = 0.003$) increases in total points scores as compared with the control group, indicating widening of the patients' functional capacities. Patients' ability to dress improved (relatives evaluated the appropriate selection of clothing in relation to season and weather, use of the correct sequence of dressing, and the ability to undress), as did the ability to use the telephone; awareness of the need for independent and correct use of medications appeared. Patients' relatives were able to leave their patients at home alone for several hours without risk of breaching safety rules.

Positive changes in the mental state of patients taking Reminyl allowed withdrawal of neuroleptics in two of four patients and dose reductions in the remainder. Antidepressants and sedatives were withdrawn or doses were reduced in every third and every fifth patient respectively. There were no changes in the doses of antiparkinsonism medications in this group of patients. In the control group, reductions in dopamine receptor agonists were needed, with withdrawal in three cases, because of increases in the severity of psychotic symptoms.

Given the theoretical consideration that parkinsonism symptoms could be increased on the background of treatment with cholinesterase inhibitors, the effects of Reminyl therapy on motor function were analyzed at each visit. We found no significant changes in total points scores on section III of the UPDRS in patients taking Reminyl, though there was a convincing positive tendency to a decrease, on average from 35.4 ± 11.8 to 32.3 ± 10.3 points ($p = 0.06$). Despite some increase in tremor in two patients of the experimental group, the mean points score for this item on the UPDRS also showed no significant change ($p = 0.3$). In the control group, there was a negative dynamic in the severity of motor impairments (increased total points from 37.2 ± 14.3 to 41.8 ± 11.7, $p = 0.048$), which might to some extent be interpreted as a result of the need to alter the doses and treatment regimes of antiparkinsonism medications.

The clinical picture of the later stages of PD is gradually supplemented by new symptoms [28], which, being motor symptoms, might have their origin in the close interrelationship with cognitive and affective disturbances. Thus, poor performance of tests for visual-spatial functions (production of visual constructs, etc.), attention, and executive functions are known to correlate with postural instability and impaired gait [37, 40]. Affective disorders (anxiety, restlessness, apathy) increase freezing. Analysis of changes in individual PD motor symptoms during Reminyl treatment revealed new patterns not previously noted in earlier studies using cholinesterase inhibitors in PD. Thus, we saw significant positive changes in gait impairments, freezing, and fall frequency in patients receiving Reminyl as compared with baseline. The mean score for "falling" on the UPDRS decreased from 2.9 ± 0.4 to 2.3 ± 0.3 ($p = 0.04$), that for "freezing" decreased from 3.0 ± 0.5 to 2.3 ± 0.4 ($p = 0.03$), and the severity of gait impairment decreased from 3.1 ± 0.4 to 2.6 ± 0.3 ($p = 0.04$). It should be noted that most of these motor symptoms responded weakly or did not respond at all to dopaminergic treatment, which emphasizes the involvement of other neurotransmitter systems in their origination.

Thus, use of Reminyl at the late stages of PD did not exacerbate the main symptoms of parkinsonism (hypokinesia, rigidity) and did not produce any changes in overall symptoms on section III of the UPDRS, though insignificant increases in tremor and drooling could be seen in some patients.

Side effects were seen in seven patients (30%) treated with galantamine, which was rather less frequent than the 47% in another trial in which the daily dose was 24 mg [4]. The following side effects were recorded: increased drooling (five patients), increased orthostatic hypotension (2), increased tremor (2), nausea (2), and urinary frequency (1). It should be noted that the severity of side effects and their

durations were insignificant and did not require any alterations in the therapeutic regime or withdrawal of the agent. Only one patient from the experimental group, receiving a galantamine dose of 16 mg/day, with an increase in orthostatic hypotension, developed urinary incontinence. The galantamine dose was decreased to 8 mg/day, and another medications were corrected (withdrawal of hypotensive agents, sedatives, and the neuroleptic Seroquel (quetiapine)). This decreased the severity of orthostatic hypotension and improved control of micturition. The galantamine dose was again increased to 16 mg/day and the patient continued to take galantamine to the end of the study period.

There is a complex dilemma in selecting treatment tactics in patients with PD and dementia complicated by psychotic disorders, between decreasing and/or withdrawing most antiparkinsonism medications and the need to prescribe antipsychotics; we can now propose a quite effective and safe route to resolving this problem – use of cholinesterase inhibitors, particularly galantamine. After stabilization of the patient's mental state, we can increase the efficacy of treatment of the motor derangements of the diseases by improving a number of levodopa-resistant changes and by providing safe increases in the doses of antiparkinsonism agents.

The timely use of treatment can delay the onset of the stage of severe dementia, allowing the patient to preserve daily activities for prolonged periods of time and decreasing the load on carers. Carers in turn can significantly decrease the economic costs of healthcare associated with prolonged admissions to the psychoneurological wards, which are indeed the most expensive.

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