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Research Article

Choline and *Ginkgo biloba* Supplementation in Adults with Asthenia and Cognitive Impairment: A Prospective Open-Label Study

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Abstract

Asthenia commonly coexists with cognitive impairment, anxiety, depressive symptoms, and sleep disturbances. Serotonergic systems modulate cholinergic activity, providing a rationale for investigating choline and *Ginkgo biloba* supplementation. This study evaluated changes in asthenic symptoms, cognition, and associated manifestations during supplementation. A prospective, open-label study included 44 adults aged 45-65 years, including 20 healthy controls; patients had asthenia and mild to moderate cognitive impairment. Choline Strong, containing choline 550 mg and standardized *Ginkgo biloba* 60 mg per capsule, was administered as one capsule twice daily for 60 days. Assessments were performed at baseline and on Days 30 and 60 using the Asthenic State Scale, Multidimensional Fatigue Inventory (MFI-20), Montreal Cognitive Assessment (MoCA), Schulte tables test, Spielberger anxiety inventory, Beck Depression Inventory, and sleep quality questionnaire. Changes across cognitive, emotional, and fatigue-related domains were evaluated to characterize the pattern and time course of clinical responses. Healthy controls provided reference values. Results were expressed as mean ± standard error. By Day 60, Asthenic State Scale scores decreased from 90.3 ± 5.2 to 55.2 ± 0.8, while MoCA scores increased from 25.4 ± 0.5 to 29.2 ± 0.1 (both $p \leq 0.01$ versus baseline). Schulte test completion time decreased from 181.3 ± 8.2 to 50.9 ± 5.6 seconds ($p \leq 0.01$). State anxiety scores decreased from 59.3 ± 2.0 to 30.2 ± 1.7, and depression scores decreased from 15.3 ± 0.8 to 9.7 ± 0.8. Sleep quality scores increased from 16.7 ± 1.2 to 20.8 ± 0.6. General, physical, and mental fatigue also improved, with changes evident by Day 30. No adverse events or treatment discontinuations were reported. Supplementation was associated with improvements in asthenia, cognition, and associated symptoms over 60 days. The open-label design and absence of a defined placebo comparator limit causal interpretation. Randomized, placebo-controlled studies are needed to confirm these findings.

Keywords: *Asthenia; Cognitive Dysfunction; Depression; Choline Strong; Choline; Ginkgo biloba; Receptors; Asthenia Assessment Scales*

Introduction

Asthenia is a pathological condition that substantially impairs quality of life and interferes with normal daily functioning. Several brain regions have been implicated in its pathogenesis. Dysfunction of neural circuits in these regions gives rise to the clinical manifestations of asthenia and associated disturbances of higher nervous activity. Receptors within these circuits are targets for agents used to treat asthenia and cognitive impairment. The principal regions and the neurotransmitter interactions within them are briefly reviewed below.

Basal ganglia: The basal ganglia include the striatum, substantia nigra, and related structures (Figure 1). Dopamine is a principal neurotransmitter in this region, where dopaminergic neurons interact predominantly with glutamatergic, GABAergic, and cholinergic pathways. Cholinergic interneurons account for only approximately 2% of striatal neurons. Nevertheless, their long projections (dendrites) receive input from virtually all brain regions, including cholinergic input from pontomesencephalic neurons and the basal forebrain, as described by P. P. Denisenko in 1980 [1]. An inverse functional interaction exists between nigrostriatal dopaminergic pathways and striatal cholinergic neurons [2]. Basal ganglia networks regulate movement, reward, and motivation [3]. In asthenia, dopaminergic activity in the striatum and prefrontal cortex decreases, potentially altering the entire network, including cholinergic interneurons, whose activity also declines. Acetylcholine (ACh) release is inversely related to D2 receptor stimulation and/or inhibition: D2 receptor antagonists reduced choline concentrations, possibly partly through its utilization for ACh synthesis, whereas D2 receptor agonists increased ACh concentrations in the hippocampus and frontal cortex [4,5]. Activation of striatal D2 receptors reduced GABA release in the globus pallidus. Although the net effect of these interactions is complex, a change in the activity of a single key neurotransmitter may alter neurotransmission throughout the basal ganglia network. Dopaminergic pathways also extend to mesocortical, mesolimbic, tuberoinfundibular, and other brain regions. Their interactions with serotonergic, GABAergic, glutamatergic, cholinergic, orexinergic, and other systems support cognition, reward, mood, movement, and neuroendocrine regulation. Receptors belonging to other neurotransmitter systems, including their subtypes, are expressed on dopaminergic neuronal membranes and regulate neuronal activity. For example, in most regions, 5-HT1A receptors enhance D2 activity, whereas 5-HT2C receptors reduce it [6].

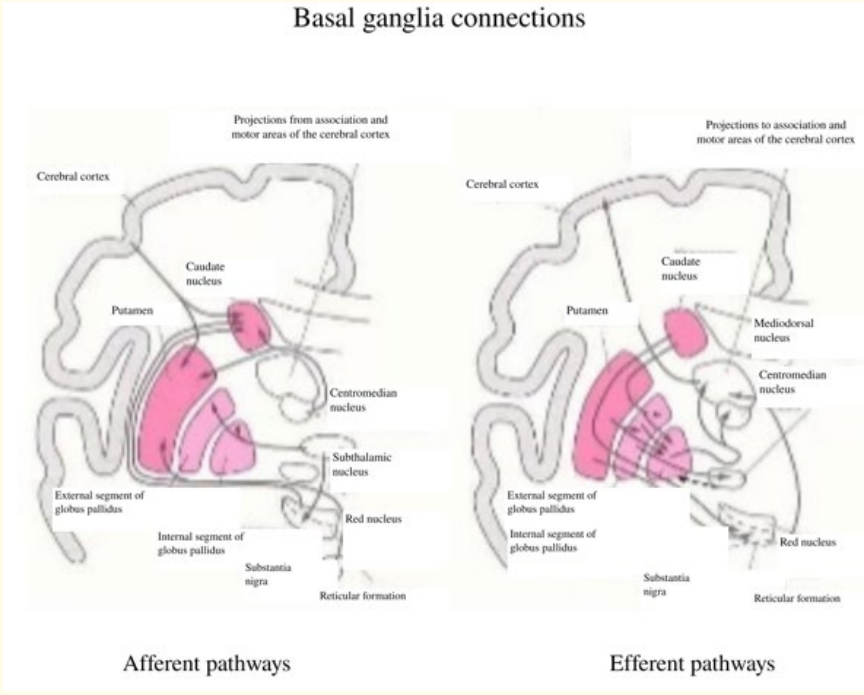


Figure 1: *Basal ganglia connections.*

Prefrontal cortex (Figure 2): The prefrontal cortex (PFC) contains interacting cholinergic, dopaminergic, corticosterone-related, NMDA receptor-mediated, and GABAA receptor-mediated neuronal systems involved in ongoing cognitive control [7]. Cholinergic neurons, particularly those of the nucleus basalis of Meynert, have a central role. Their projections ascend to the cortex and hippocampus, where they sustain attention and stabilize functional activity [2], thereby supporting memory encoding. In the hippocampus, cholinergic neurons also modulate basal ganglia dopaminergic activity, as described above, and interact closely with serotonergic neurons, releasing their neurotransmitters into a shared extracellular space [8].

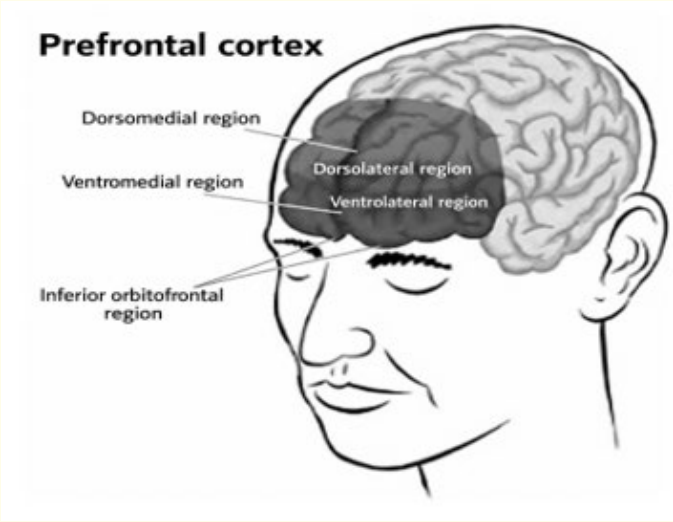


Figure 2: *Prefrontal cortex.*

NMDA receptor signaling is another important contributor to asthenia in this region. Asthenia is thought to be associated with clear evidence of hypocatabolism and NMDA receptor hypofunction [9]. Dysfunction in this region is linked to the severity of asthenia, particularly in older adults with marked cognitive impairment, largely because of reduced receptor density and slower synaptic transmission [7]. These changes are essentially manifestations of neuroinflammation followed by neurodegeneration. Associated markers include accumulation of glial fibrillary acidic protein (GFAP), described as an inducer of neuroinflammation, and activation of the mitogen-activated protein kinase pathway, MAPK/ERK [10]. Importantly, cholinergic signaling through M1 receptors enhances NMDA receptor responses to glutamate, contributing to long-term potentiation between neurons. This is considered a key mechanism of neuronal plasticity and, in our view, the neurochemical basis of memory.

In addition to NMDA receptor signaling, cortisol has an important role in PFC dysfunction associated with asthenia and cognitive decline, particularly in individuals who consume alcohol. Cortisol enhances noradrenergic effects, which is especially relevant in patients taking norepinephrine reuptake inhibitor antidepressants. It impairs neuroplasticity while adapting the body to a state of excessive vigilance at the expense of its reserves. The sense of invulnerability described in colloquial language has been attributed to cortisol [11]. Cholinergic neurons are placed under sustained demand as they counteract excessive cortisol effects and support vigilance and cognitive flexibility. By stimulating ACh release from presynaptic PFC terminals, cortisol depletes ACh stores. Reduced neuroplasticity and cognitive rigidity follow, with bradyphrenia, impaired concentration and memory, and difficulty processing information; alcohol-related inappropriate humor may also occur in individuals who drink. The brain's adaptive capacity consequently decreases. Clinically, this is manifested by slow functional recovery and fatigue that does not resolve with rest. Cholinergic neurons projecting to the PFC are among the most extensively arborized neurons in the central nervous system; in humans, the total arbor length of a single neuron may approach 100m [12]. Cholinergic projections to the hippocampus, hypothalamus, amygdala, and PFC exhibit circadian rhythmicity, releasing ACh predominantly during sleep. This is thought to contribute to memory consolidation [13].

Anterior cingulate cortex (Figure 3): The anterior cingulate cortex (ACC) supports higher-order functions, including sustained motivation and volition, energy allocation, goal-directed attention, reward anticipation, and decision-making. These functions depend on interactions among multiple receptor systems and autocoids. We therefore describe asthenia as autocoidosis: within the ACC, which functions as a major hub, a single cholinergic or other neuron may simultaneously receive several ergotropic and trophotropic synaptic inputs [2], providing opposing regulation of multiple functions [14]. This complexity makes it difficult to predict the appropriate direction of pharmacological intervention and can lead to incorrect therapeutic choices. Chronic stress reduces ACC volume, effectively resulting in neuronal loss, particularly of von Economo neurons, which contain cholinergic fibers and support complex problem-solving, error detection, empathy, self-control, and appropriate social behavior [15]. Inflammatory activity in microglia and astrocytes initiates neuroinflammation.

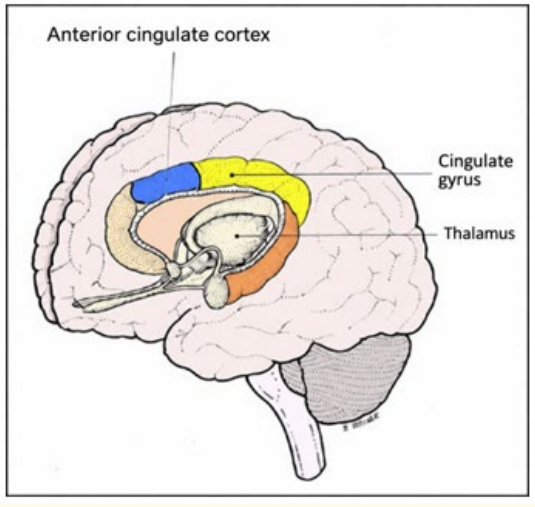


Figure 3: *Anterior cingulate cortex.*

Hypothalamus (Figure 4): The hypothalamus contains diverse cell populations with complex neurochemical profiles, including neurotransmitter, peptide, and cytokine systems. It regulates sleep, stress, motivated behavior, and energy balance within the brain's autocoid systems. Disruption of its synaptic circuits leads to chronic exhaustion [16]. The hypothalamus links the nervous and endocrine systems, and its role in maintaining homeostasis reflects this interaction. Individuals with high cortisol levels, including men who regularly consume beer, tend to have difficulty understanding spoken language and exhibit excessive self-confidence. Cortisol disrupts hypothalamic function and depletes its cholinergic pool, seemingly reducing the perceived significance of past events. This effect is used in cognitive behavioral therapy for asthenia associated with depression [17], as such therapy reduces activity in the amygdala, another structure implicated in asthenia.



Figure 4: *Hypothalamus.*

Amygdala (Figure 5): The amygdala processes both positive and negative emotions, including those associated with fear, danger, stress, and anxiety [8], and evaluates threats in relation to fight-or-flight responses. Its location in the medial temporal region, anterior to the hypothalamus, allows it to receive information from all sensory modalities and to communicate rapidly and bidirectionally with subcortical structures and the cerebral cortex [2]. It also receives inhibitory input from the ventral striatum and frontal cortex. The amygdala has an important role in activating the hypothalamic-pituitary-adrenal axis, particularly during stress. In individuals with isolated amygdala lesions, as in Urbach-Wiethe syndrome, responses to frightening and life-threatening stimuli are absent. The amygdala is also important in social interaction, enabling recognition of emotional cues from the eyes, facial expressions, and other facial movements [18]. It is considered a principal neurobiological correlate of social anxiety disorder [19]. Serotonin predominates among its neurotransmitter systems, with 5-HT1A, 5-HT2, 5-HT3, 5-HT4, and 5-HT6 receptor subtypes represented; 5-HT2 receptors have the highest density [8]. Testosterone-related signaling and corticotropin-releasing hormone (CRH) receptors also have important roles. CRH receptors initiate fear and its behavioral manifestations, including flight, fight, and freezing. Cholinergic systems regulate baseline amygdala activity and hippocampal-amygdala interactions [20].

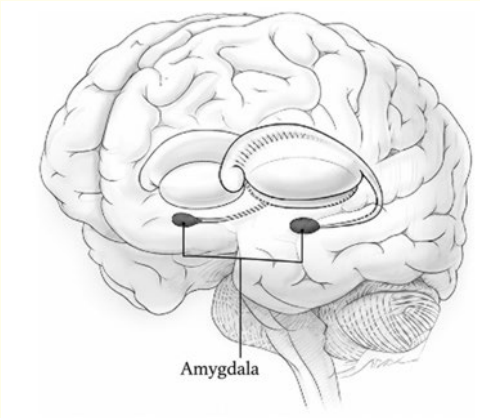


Figure 5: *Amygdala.*

Thus, neurotransmitter, hormonal, and cytokine systems contribute to the pathogenesis of asthenia and cognitive dysfunction. Cholinergic systems have a distinctive, possibly modulatory role. It was therefore of interest to investigate the therapeutic effects of Choline Strong, a preparation with cholinergic and serotonergic components, in asthenia and cognitive dysfunction.

Objective of the Study

To investigate the therapeutic effects of Choline Strong in asthenia accompanied by moderate cognitive impairment.

The study objectives were to:

- Assess the therapeutic efficacy of Choline Strong using standardized measures of asthenia, cognition, depression, sleep quality, and other outcomes, as described below, in comparison with a placebo group.
- Identify the measures showing the largest changes.
- Describe the principal elements of the mechanism of action of Choline Strong in asthenia associated with cognitive dysfunction.

Methods

The study was conducted at the Department of Neurology of Pavlov First Saint Petersburg State Medical University and at I. I. Mechnikov North-Western State Medical University. This open-label, prospective study included 44 participants, of whom 20 were healthy

volunteers serving as controls. Participants were men and women aged 45-65 years; the patient group had asthenic syndrome with neurological manifestations consisting of mild to moderate cognitive impairment and asthenic and depressive symptoms. Changes in outcome measures were compared with values in healthy volunteers. Choline Strong was administered as one capsule twice daily.

Patients were selected according to the clinical inclusion and exclusion criteria shown in table 1. Cognitive impairment and its severity were assessed using established scales, including the MoCA, with a minimum score of 25. Other assessments included the Asthenic State Scale (ASS), the Spielberger anxiety inventory, the Beck Depression Inventory, the Schulte tables test of attention, and a sleep quality questionnaire. Physicians and patients also provided subjective assessments of treatment efficacy using specifically developed questionnaires.

Neuropsychological assessments and laboratory tests were performed on Day 1, before initiation of Choline Strong or placebo, on Day 30, and on Day 60, at the end of treatment. Patients were selected on the basis of complaints of impaired memory and attention, asthenia, anxiety, and sleep disturbance. The assessment criteria included scores of 15-50 on either Spielberger subscale, an asthenia scale score greater than 50, and a sleep quality score greater than 9.

Criteria	Description
Inclusion criteria	Age 45-65 years. Complaints of memory decline and forgetfulness. Reduced concentration and mental performance. Increased fatigability during mental and/or physical work compared with previous functioning. MoCA score ≥25. Patient informed consent.
Exclusion criteria	Contraindications to Choline Strong, including intolerance to its ingredients, pregnancy, and breast-feeding. Marked cognitive impairment (MoCA <25), or cognitive impairment that interferes with occupational, social, or daily activities even when the MoCA score exceeds 25. Cognitive impairment due to metabolic disorders (vitamin B12 or folate deficiency), neurodegenerative disease (Alzheimer disease or parkinsonism), or sequelae of anticholinergic intoxication. Epilepsy, traumatic brain injury, psychiatric disorders, substance dependence, or withdrawal syndromes. Severe or decompensated somatic disease, pregnancy, or breastfeeding. Use within 2 weeks before study initiation of agents with antioxidant, antihypoxic, nootropic, energy-producing, or other metabolic effects, including cytoflavin, mexidol, meldonium, carnicetine, cerebrolysin, actovegin, instenon, cortexin, piracetam, semax, choline alfoscerate preparations, idebenone, memantine, and related agents.

Table 1: *Inclusion and exclusion criteria.*

Data were analyzed using SPSS 12RU and are presented as mean ± standard error. Between-group comparisons of scale scores were performed using the Mann-Whitney test, with $p = 0.05$ as the significance threshold.

The study was approved by the local ethics committee. All participants provided written informed consent.

Results

All patients tolerated treatment well. No adverse events or discontinuations of choline strong were recorded, supporting a favorable safety profile for the preparation.

Choline Strong, administered as one capsule twice daily for 60 days, was associated with substantial clinical improvement on neuropsychological testing (Table 2).

#	Measure	Day 1	Day 30	Day 60	Control
1	Asthenic State Scale (ASS)	90.3 ± 5.2 102.1-79.8	75.1 ± 5.4 87.9-62.3	55.2 ± 0.8* 57.34-55.06	39.1 ± 2.7 45.55-32.65
2	Sleep quality questionnaire	16.7 ± 1.2 19.3-14.1	17.4 ± 1.12 20.3-14.7	20.8 ± 0.6* 22.1-19.5	22.3 ± 0.6 23.63-20.43
3	Autonomic symptoms questionnaire	42.3 ± 1.6 46.16-38.44	37.8 ± 2.2 43.3-32.3	20.1 ± 1.7* 24.39-15.81	9.2 ± 0.3 10-8.4
4	Beck Depression Inventory	15.3 ± 0.8 17.3-13.3	14.7 ± 0.6 16.3-13.1	9.7 ± 0.8* 11.7-7.7	6.2 ± 0.7 7.9-4.49
5	Spielberger anxiety inventory State anxiety	59.3 ± 2.0 64.4-54.1	44.1 ± 1.8* 48.5-39.7	30.2 ± 1.7* 34.49-25.91	17.7 ± 0.92 20.0-15.4
6	Spielberger anxiety inventory Trait anxiety	59.3 ± 2.6 59.3-46.47	48.2 ± 2.2 53.4-43.0	45.1 ± 1.6** 48.96-41.24	18.1 ± 1.2 20.8-15.4
7	Montreal Cognitive Assessment (MoCA)	25.4 ± 0.5 26.65-24.15	27.8 ± 0.4** 28.7-27.0	29.2 ± 0.1* 29.46-28.9	29.6 ± 0.12 29.9-29.3
8	Attention assessment Schulte tables test (s)	181.3 ± 8.2 200.6-162.0	113.2 ± 7.1* 130.4-96.0	50.9 ± 5.6* 63.34-37.2	38.2 ± 3.3 46.39-30.1

Table 2: *Neuropsychological assessment results during choline strong treatment.*

*Values are presented as mean ± standard error (M ± m). Statistical significance is relative to Day 1: *p ≤ 0.01; **p ≤ 0.05.*

At baseline, Asthenic State Scale scores were reported to be three times the control values (90.3 ± 5.2 vs 39.1 ± 2.7 points, respectively), corresponding to moderate (76-100 points) or severe (101-120 points) asthenia. After 30 days of Choline Strong, one capsule twice daily, the score decreased by a reported 26% from baseline to 75.1 ± 5.4 points. By Day 60, it had decreased to 55.2 ± 0.8 points (p ≤ 0.01), a reduction described as almost one-half (39%) from baseline and a value only 30% above the control score (Figure 6).

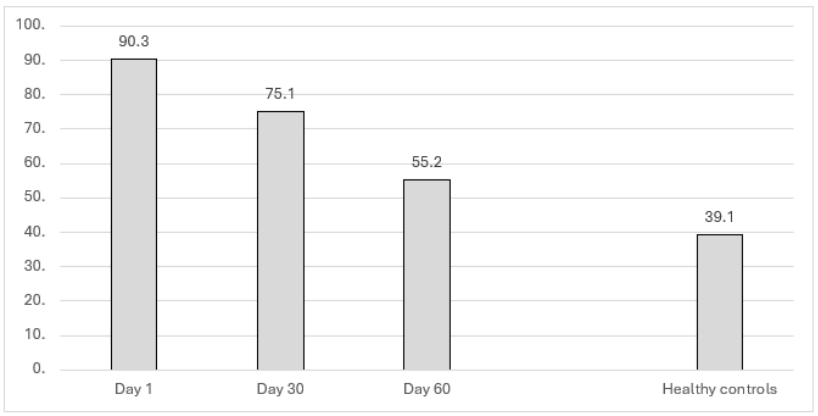


Figure 6: *Changes in asthenic state scale scores during choline strong treatment.*

The sleep quality questionnaire identified moderate disturbances in sleep initiation, nocturnal awakenings, and satisfaction with sleep. The baseline score was 16.7 ± 1.2 points, compared with 22.3 ± 0.6 in controls (Figure 7). By Day 30, the score had increased by only 5% to 17.4 ± 1.12 points. By Day 60, it reached 20.8 ± 0.6 points, reported as 20% above baseline and only 7% different from the control value. Sleep latency and the number of nocturnal awakenings decreased, while sleep duration and daytime well-being improved.

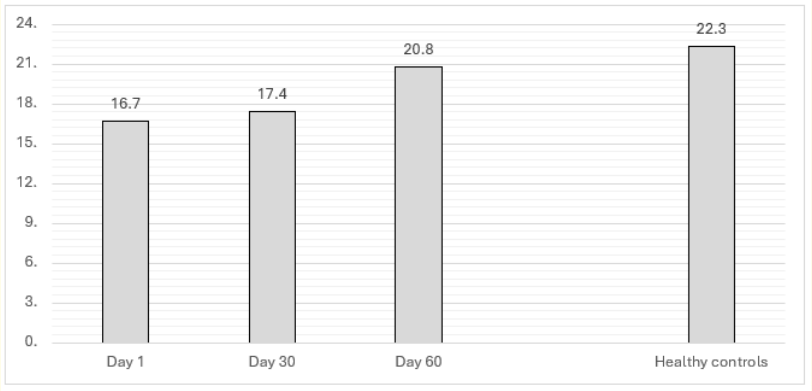


Figure 7: *Changes in sleep quality scores during choline strong treatment.*

Autonomic symptoms also decreased substantially. Baseline scores were 4.5 times the normal values (42.3 ± 1.6 vs 9.2 ± 0.3 points, respectively). By Day 60 of choline strong treatment, the score had decreased approximately twofold to 20.1 ± 1.7 points, reported as differing by 55% from the control value of 9.2 ± 0.3 points.

No change in Beck Depression Inventory scores was identified on Day 30. A statistically significant change was observed on Day 60, when the depression score was approximately 1.5-fold lower, a reported reduction of 39%. Nevertheless, the control group score remained 36% lower than the Day 60 treatment-group score.

Baseline state anxiety on the Spielberger-Hanin inventory was 59.3 ± 2.0 points, nearly 3.5 times the control value of 17.7 ± 0.92 points, indicating high anxiety. This finding is consistent with reports that anxiety and depressive disorders commonly accompany chronic somatic disease and contribute to reduced quality of life in patients with asthenia. The state anxiety score decreased significantly by a reported 36% by Day 30 ($p \leq 0.01$) and reached 30.2 ± 1.7 points on Day 60 ($p \leq 0.01$), reported as differing by 42% from controls and interpreted as mild anxiety. Trait anxiety showed only a trend toward improvement: scores were 59.3 ± 2.6, 49.2 ± 2.7, and 45.1 ± 1.6 points, compared with a normal value of 18.1 ± 1.2 points. These findings reflect the high baseline anxiety in patients with asthenia and the reported difficulty in correcting it.

On Day 1, the mean MoCA score was 25.4 ± 0.5 points, interpreted as mild to moderate cognitive impairment and reported as differing by 15% from controls. By Day 30, the mean score increased to 27.8 ± 0.4 points, a 9% change from baseline ($p = 0.05$). By Day 60, it reached 29.2 ± 0.1 points, a 14% change from baseline ($p \leq 0.01$), and was not statistically different from the control value of 29.6 ± 0.12 points (Figure 8).

On the Schulte tables test, baseline task completion time was 181.3 ± 8.2 seconds, reported as 79% longer than the normal value of 38.2 ± 3.3 seconds (Table 2). By Day 30, attentional performance improved by 38% ($p = 0.05$). By Day 60, improvement reached 72%

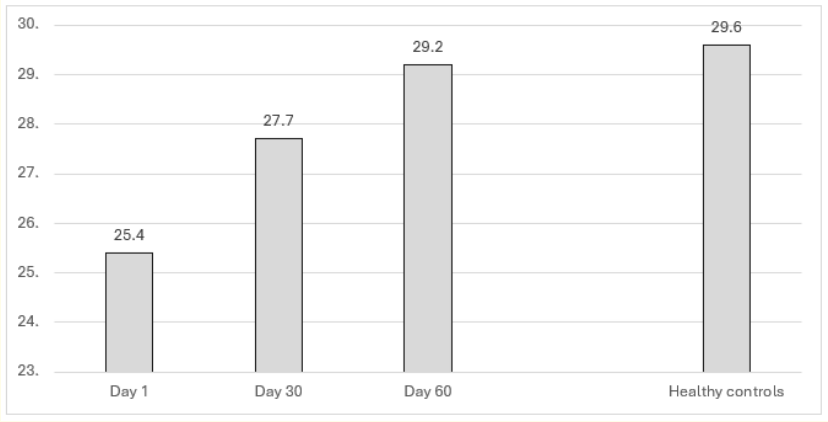


Figure 8: *Changes in Montreal Cognitive Assessment (MoCA) scores during choline strong treatment.*

relative to baseline and 56% relative to Day 30 (p = 0.05; Table 2). Despite this progressive improvement, performance remained 26% below the normal level: task completion time was 50.9 ± 5.6 seconds versus 38.2 ± 3.3 seconds in controls.

Analysis of individual MoCA domains (Table 3) identified particularly marked impairment in visuoconstructional and executive skills, with a baseline score of 3.01 ± 0.45 points out of 5. Seventy percent of participants did not understand the number-letter alternation task, and 75% could not draw a clock. Attention was also impaired: 78% scored zero on Day 1 and could not repeat digit sequences either forward or backward; the mean score was 1.11 ± 0.04 points out of 2. For verbal fluency, 75% scored zero on Day 1, naming fewer than 11 words beginning with the specified letter within 1 minute; the mean score was 0.33 ± 0.015 points out of 1. Delayed recall was 1.90 ± 0.15 points out of 5; 30% of patients scored zero on Day 1 and could not recall any words. During Choline Strong treatment, visuoconstructional and executive scores increased to 3.97 ± 0.46 on Day 30 and 4.28 ± 0.25 on Day 60. The Day 60 score did not differ from the control value of 4.3 ± 0.1 points (Table 3).

The attention domain, in which digit repetition was most affected, improved by a reported 30% to 1.56 ± 0.03 points on Day 30 and by 38% to 1.79 ± 0.09 points on Day 60. Seventy-nine percent of participants could repeat digits forward, and 58% could repeat them backward.

Verbal fluency improved significantly by a reported 38% to 0.53 ± 0.02 points on Day 30 and by 66% to 0.74 ± 0.03 points on Day 60. Seventy-nine percent of patients named more than 11 words.

Delayed recall reached 3.2 ± 0.13 points on Day 30 (41%) and 3.45 ± 0.12 points on Day 60 (45%). Thirty percent of participants recalled all five words, and 76% recalled four words (p < 0.01).

Measure	Day 1	Day 30	Day 60	Control
Visuoconstructional and executive skills	3.01 ± 0.45 4.04-2.02	3.97 ± 0.46 5.06-2.88	4.28 ± 0.25 5.07-3.49	4.3 ± 0.1 4.56-4.04
Attention	1.11 ± 0.04 1.19-1.17	1.56 ± 0.03* 1.63-1.49	1.79 ± 0.09* 1.83-1.75	1.8 ± 0.1 2.06-1.54
Verbal fluency	0.33 ± 0.015 0.37-0.29	0.53 ± 0.02* 0.58-0.48	0.74 ± 0.03* 0.81-0.67	0.8 ± 0.02 0.87-0.73
Delayed recall	1.90 ± 0.15 2.26-1.5	3.2 ± 0.13* 3.55-2.85	3.45 ± 0.12* 3.75-3.15	4.3 ± 0.12 4.6-4.0

Table 3: *Changes in individual MoCA domain scores during choline strong treatment.*

*Values are presented as mean ± standard error (M ± m). Statistical significance is relative to Day 1: *p ≤ 0.01; **p ≤ 0.05.*

In addition to assessing overall asthenia, we examined the pattern of asthenic symptoms to characterize the effects of Choline Strong. Patients completed the Multidimensional Fatigue Inventory (MFI-20), which provides a subjective quantitative assessment of overall fatigue severity and its individual manifestations (Table 4).

#	Measure	Day 1	Day 30	Day 60	Control
1	General Fatigue	15.2 ± 1.16 17.96-12.44	11.6 ± 0.53** 12.89-10.31	9.8 ± 0.66* 11.4-8.16	7.6 ± 0.62 9.3-5.9
2	Reduced Activity	12.87 ± 1.01 15.39-10.35	8.2 ± 0.5* 9.4-7.0	7.8 ± 0.8* 9.7-5.9	6.8 ± 0.80 8.7-4.9
3	Reduced Motivation	10.10 ± 0.78 12.09-8.11	8.76 ± 0.89 10.97-6.55	8.09 ± 0.81 10.19-6.89	7.7 ± 0.88 9.84-5.56
4	Physical Fatigue	12.88 ± 0.75 17.3-13.3	10.8 ± 0.55* 11.9-9.7	8.9 ± 0.4* 10.1-7.7	6.9 ± 0.76 8.8-5.0
5	Mental Fatigue	12.23 ± 0.68 13.85-10.61	9.91 ± 0.4** 10.71-9.11	8.2 ± 1.52* 9.72-8.68	6.8 ± 066 8.2-5.4

Table 4: *MFI-20 domain scores during choline strong treatment. Values are presented as mean ± standard error (M ± m). Statistical significance is relative to Day 1: *p ≤ 0.01; **p ≤ 0.05.*

On Day 1, the MFI-20 General Fatigue score was 15.2 ± 1.16 points, reported as 50% higher than the control value. By Day 30 of Choline Strong treatment, general fatigue decreased by 24% relative to Day 1 (p = 0.05). By Day 60, the reduction reached 36%. However, the difference between Days 30 and 60 was not statistically significant, indicating only a trend toward further improvement. A similar pattern was observed for Reduced Activity: the initial improvement in activity, reported as 36% above baseline, stabilized by Day 30 and remained within a similar range on Day 60 (Table 4; Figure 9). The largest changes in Reduced Motivation also occurred by Day 30 and persisted through the end of the study, although they were not statistically significant (Table 4). Clear, statistically significant changes were observed in Physical Fatigue and Mental Fatigue. Marked improvements were recorded after 30 days, with reported reductions of 27% and 29%, respectively (p = 0.05), followed by further clinical improvement. By the end of follow-up, physical fatigue decreased by 31% and mental fatigue by 33% relative to baseline (p = 0.01; Figure 9). Almost all patients reported improved well-being, greater capacity for intellectual work, and both the desire and ability to undertake physical activity.

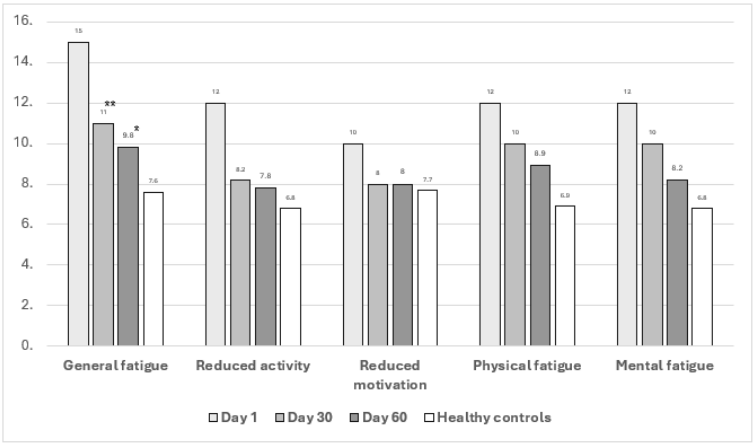


Figure 9: *MFI-20 domain scores during choline strong treatment. Statistical significance relative to Day 1 is reported in table 4.*

Discussion

Every physiological function is influenced by positive and negative regulators: biologically active substances, or autocoids, that enhance or suppress it. Memory and cognitive dysfunction are no exception. The theory of autocoidosis proposed by Yu. V. Natochin in 2022 may therefore provide a pathochemical basis for identifying and investigating agents for the treatment of asthenia and cognitive dysfunction (Figure 10).

Of the systems shown in figure 10, we examined three trophotropic systems involved in the proposed effects of Choline Strong: the cholinergic, serotonergic, and α2-adrenergic systems. Choline Strong combines choline bitartrate, an ACh precursor, with *Ginkgo biloba*, described as having affinity for 5-HT1A and α2 receptors. These receptors contribute substantially to the neurochemical basis of learning, memory, and mood in the relevant brain regions discussed in the Introduction. We did not directly measure autocoid concentrations; instead, we assessed their effects on cognition, memory, and learning using standardized questionnaires.

Asthenia measures, including the Asthenic State Scale and MFI-20, may be viewed as reflecting the neurochemical disturbances associated with asthenia and cognitive dysfunction. They quantify symptoms arising from cholinergic, serotonergic, dopaminergic, and noradrenergic dysfunction and the development of neuroinflammation. Asthenic State Scale scores improved clearly on Days 30 and 60, with reported reductions in asthenia of 26% and 55.2%, respectively, in almost all patients. Within the proposed interpretation of the MFI-20 domains, Physical Fatigue and Mental Fatigue reflect reduced dopaminergic activity, particularly in the PFC [2], and serotonergic imbalance.

Ergotropic systems

System	Associated effects
Adrenergic systems	Metabolic disturbances
Noradrenergic systems	Excitation; hypertension
Dopaminergic systems	Deviant behavior; overproduction
Glutamatergic systems	Amnesia; seizures
Histaminergic systems	Overproduction; hemodynamic disturbances
Neurotensinergic systems	Hemodynamics; inflammation
Leukotrienergic systems	Degenerative and inflammatory reactions
Cholinergic systems	Cognition; behavior; movement; hemodynamics; immunity

Trophotropic systems

System	Associated effects
Glycinergic systems	Sedation; reduced tone
Adenosinergic systems	Sedation; increased tone
GABAergic systems	Sedation; anxiolysis; reduced tone
Serotonergic systems	Drive; empathy; anxiolysis
Opioidergic systems	Antinociception; drive; dysphoria
Cholecystokinin systems	Anxiety; cognition
Cholinergic systems	Cognition; behavior; movement; hemodynamics; immunity

Autocoid systems with an undetermined direction of effect in asthenia

Cytokine, neurotensin, vasopressin, eicosanoid, endothelin, incretin, orexin, relaxin, estrogen, androgen, and other regulatory autocoid systems of the human body.

Figure 10: *Ergotropic (activating) and trophotropic (inhibitory) systems involved in asthenia and cognitive impairment [11]. Trophotropic systems are shaded.*

Reduced Activity, Reduced Motivation, and general somatic manifestations reflect serotonin imbalance or deficiency and altered GABA turnover in close interaction with cholinergic systems. General Fatigue reflects relationships among choline, GABA, and serotonin. General fatigue decreased significantly by 24% on Day 30 and 36% on Day 60 relative to Day 1 ($p = 0.05$). There was no statistically significant difference between Days 30 and 60, indicating that the greatest reduction occurred during the first 30 days. Improvements in activity and motivation were also greatest by Day 30, reported as 36% and 25%, respectively, after which the measures stabilized through the end of follow-up. Despite this stabilization, patients reported stable mood, increased energy, and improved vitality. Significant and substantial improvements in Physical Fatigue and Mental Fatigue were evident by Day 30 and continued through Day 60 (Figure 9). By Day 60, virtually all MoCA measures, including constructional and executive skills, verbal fluency, and delayed recall, improved in every patient; the reported improvements were 1.4-, 1.2-, 1.5-, and 1.8-fold. The largest changes were observed on the Schulte tables test, with 1.6-fold and 3.6-fold improvements on Days 30 and 60, respectively. Thus, Choline Strong showed therapeutic effects on asthenia and cognitive dysfunction at both assessment points, supporting the need for prolonged administration.

Neurotransmitter interactions in the basal ganglia, PFC, ACC, and particularly the hippocampus are organized according to a receptor-hub principle. ACh and serotonin (5-HT) support both synaptic and extrasynaptic interactions within networks of the hippocampus, striatum, substantia nigra, and other structures involved in learning, memory, and other functions [21]. Furthermore, 5-HT1A receptors, often located presynaptically on cholinergic terminals [2], modulate cholinergic neuronal activity. In the proposed model, they activate these neurons and promote action potential generation as ACh availability increases. Choline is the principal substrate for ACh synthesis, since the other component, acetyl coenzyme A (acetyl-CoA), is described as consistently available in sufficient quantities.

Accordingly, a cholinergic neuron stimulated by serotonin becomes active and generates action potentials. With choline and acetyl-CoA available, cholinergic neurons increase choline uptake through specific transporters, rapidly synthesize ACh, and enhance its release within hippocampal circuits and, through their projections, other brain regions. These effects support cognition, memory, learning, and motor activity; the latter is attributed to cholinergic signaling in skeletal muscle proprioceptors. In this model, the *Ginkgo biloba* component of Choline Strong increases hippocampal demand for its other component, choline, through 5-HT1A receptors, thereby activating the cholinergic component of hippocampal neural networks [22]. The proposed mechanism can be illustrated by the following analogy.

Consider an academic department producing a pharmaceutical product as an analogy for a cholinergic neuron.

- Choline represents the reagents used by the department to synthesize the product.
- ACh represents the finished product released by the department.
- Serotonin represents the department head, who signals that more ACh is required.
- In response, the department, representing the cholinergic neuron, increases synthesis and produces more ACh.

At the systems level, reduced anxiety and improved mood, attributed to serotonin, allow the hippocampus to adopt a state favorable to learning and plasticity, supported by ACh, and to process information normally. In the analogy, efficient production through ACh is supported by effective management through 5-HT, creating a favorable functional environment. In our view, this is the most important element of the proposed mechanism of action of choline strong.

All patients tolerated choline strong very well. No adverse events or treatment discontinuations were recorded. This observation is consistent with the toxicity data for the preparation and suggests a favorable safety profile.

Conclusion

Asthenia and cognitive dysfunction may usefully be considered forms of autocoidosis. This approach offers opportunities to identify and investigate new pharmacological strategies for these conditions.

Choline strong demonstrated high clinical efficacy in patients with asthenia and cognitive dysfunction below the threshold for dementia.

Choline strong administration was associated with substantial improvements in cognitive measures across all scales and tests used, including attention and concentration, working memory, and information processing speed, on both Days 30 and 60.

Choline strong administration was accompanied by reductions in overall asthenia and its physical and mental components from Day 30 through Day 60, supporting the need for prolonged administration.

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