

Noopept

A proline-glycine dipeptide cognitive enhancer (GVS-111) developed at the Zakusov Institute of Pharmacology in Russia, distinguished from classical racetam nootropics by approximately 1000-fold greater mass potency, rapid conversion to the endogenous neuropeptide cycloprolylglycine, and a multifactorial mechanism encompassing AMPA receptor positive allosteric modulation, NMDA receptor modulation, NGF and BDNF upregulation, HIF-1 transcription factor activation, and neuroprotection against amyloid-beta toxicity and tau hyperphosphorylation.

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Synthetic dipeptide nootropic and neuroprotectant derived from cycloprolylglycine with AMPA receptor positive allosteric modulation and neurotrophic factor upregulation

ABSTRACT

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Noopept (INN: omberacetam; development code GVS-111; N-phenylacetyl-L-prolylglycine ethyl ester; CAS 157115-85-0; molecular formula C₁₇H₂₂N₂O₄; molecular weight 318.37 g/mol) is a synthetic dipeptide nootropic and neuroprotectant developed in the mid-1990s at the V.V. Zakusov Research Institute of Pharmacology of the Russian Academy of Medical Sciences by Tatyana Gudasheva, Rita Ostrovskaya, and Sergei Seredenin using a drug-based peptide design strategy that models the pyrrolidone ring of piracetam as the central element of a beta-turn dipeptide. The compound is approved in the Russian Federation (registration 2006) and several former Soviet states for the treatment of cognitive impairment of vascular and post-traumatic origin at oral doses of 10 to 30 mg per day, doses approximately 1000-fold lower by mass than the effective doses of piracetam (1200 to 4800 mg per day), its structural prototype. Noopept is not approved by the United States Food and Drug Administration, the European Medicines Agency, or the regulatory authorities of Japan, Australia, or Canada. It is sold internationally as a research-grade compound and as an unregulated dietary supplement in several jurisdictions.

The pharmacological mechanism of noopept is multifactorial and operates through both the parent compound and its principal active metabolite, cycloprolylglycine (cyclo-L-prolylglycine, CPG), an endogenous brain dipeptide. The parent compound and CPG function as positive allosteric modulators of AMPA-subtype ionotropic glutamate receptors, increasing glutamate sensitivity without direct agonist binding. Noopept modulates NMDA

receptor expression and function, upregulates the expression of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in hippocampal and cortical neurons on chronic administration, activates the transcription factor hypoxia-inducible factor 1 (HIF-1) through inhibition of prolyl hydroxylase, and provides direct neuroprotection against amyloid-beta peptide toxicity, glutamate excitotoxicity, oxidative stress, and calcium overload in cellular and animal models. In Alzheimer's disease cellular models, noopept attenuates tau hyperphosphorylation at Ser396 and reduces apoptosis through suppression of the mitochondrial apoptotic pathway.

Pharmacokinetics in humans are characterized by rapid oral absorption (time to peak plasma concentration approximately 15 to 20 minutes), extensive first-pass metabolism yielding an oral bioavailability of approximately 10 percent relative to parenteral administration, rapid hydrolysis of the parent ester to the active metabolite cycloprolylglycine, and a short plasma half-life of the parent compound. The pharmacological effect persists for 3 to 6 hours after oral dosing, substantially longer than the plasma residence of the parent compound, consistent with the contribution of the longer-lived CPG metabolite and downstream transcriptional effects on neurotrophic factor expression. The compound does not appear to undergo significant cytochrome P450-mediated metabolism; the principal biotransformation is peptidase-mediated ester hydrolysis and amide cleavage.

The clinical evidence base is concentrated in Russian-language literature and is modest by Western regulatory standards. The principal English-language clinical study is the Neznamov and Teleshova (2009) comparative trial of noopept (20 mg per day) and piracetam (1200 mg per day) in 53 patients with mild

cognitive disorders of vascular and traumatic origin over 56 days, which demonstrated comparable cognitive improvement with a 1.8-fold lower incidence of adverse events in the noopept arm. Preclinical evidence is more extensive, spanning rodent models of ischemic brain injury, Alzheimer's disease (both amyloid-beta infusion and transgenic models), traumatic brain injury, and age-related cognitive decline. The compound is well tolerated at recommended doses; the principal adverse events are sleep disturbance, irritability, and transient blood pressure elevation, all at low incidence. No serious adverse events have been reported in published clinical studies at doses up to 30 mg per day for periods up to 56 days. Long-term safety data beyond 56 days of continuous administration are not available.

This monograph reviews the chemistry, synthesis, and structural pharmacology of noopept; the multifactorial mechanism of action including AMPA receptor modulation, NMDA receptor effects, neurotrophic factor upregulation, HIF-1 activation, and amyloid-beta neuroprotection; the pharmacokinetic profile with emphasis on the cycloprolylglycine metabolite; the preclinical pharmacology across ischemic, neurodegenerative, and traumatic models; the clinical evidence base; sourcing and quality verification; reconstitution and handling; stack interactions and combinations; adverse events and safety signal; and a comparative assessment of five nootropic alternatives (piracetam, aniracetam, phenylpiracetam, semax, and cerebrolysin) against noopept on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Omberacetam.

Common name: Noopept. The trade name Noopept is the canonical identifier in the Russian Federation registration and in the international research literature. The compound is also referenced as GVS-111 in the early pharmacology and pharmacokinetics literature from the Zakusov Institute [1, 2].

Development code: GVS-111 (V.V. Zakusov Research Institute of Pharmacology, Russian Academy of Medical Sciences).

Chemical Abstracts Service registry number: 157115-85-0.

International Union of Pure and Applied Chemistry name: Ethyl 2-[[[(2S)-1-(2-phenylacetyl)pyrrolidine-2-carbonyl]amino]acetate. Alternative systematic names include N-phenylacetyl-L-prolylglycine ethyl ester and ethyl N-(N-phenylacetyl-L-prolyl)glycinate.

PubChem CID: 180496.

Marketed names: Noopept (JSC LEKKO Pharmaceuticals, Russian Federation). Generic preparations are available from multiple Russian pharmaceutical manufacturers. The compound is not marketed under trade names outside the Russian Federation and former Soviet states; international availability is as a research compound or unregulated supplement.

1.2 Structural class and chemistry

Noopept is a synthetic dipeptide derivative consisting of L-proline and glycine in a linear dipeptide configuration, with the proline nitrogen acylated by phenylacetic acid and the glycine carboxyl group esterified as the ethyl ester. The compound is structurally a modified Pro-Gly dipeptide and was designed as a peptide analog of piracetam (2-oxo-1-pyrrolidineacetamide) based on the hypothesis that the pyrrolidone ring of piracetam could be topologically represented as the central element of a beta-turn in a short peptide [3, 4].

Molecular formula: C₁₇H₂₂N₂O₄.

Exact mass: 318.1580 g/mol (monoisotopic).

Molecular weight: 318.37 g/mol.

Physical properties: White to off-white crystalline powder. Melting point 94 to 98 degrees Celsius. Predicted boiling point approximately 547 degrees Celsius. Predicted density approximately 1.20 g/cm³. Optical rotation [α]_D of -115 to -125 degrees (c = 0.5 in chloroform). Soluble in dimethyl sulfoxide (up to 25 mg/mL), sparingly soluble in water, soluble in ethanol and methanol. The compound is stable as a dry powder at room temperature and under refrigeration.

Stereochemistry: Noopept contains one stereocenter at carbon 2 of the proline ring and is supplied as the single (2S) enantiomer corresponding to L-proline. The glycine residue is achiral. Investigators should confirm the correct stereochemical configuration by optical rotation or chiral chromatography, as the D-proline analog has not been characterized for nootropic activity and would represent a degradation or synthesis impurity.

1.3 Synthesis

The synthesis of noopept proceeds through peptide coupling chemistry and has been reported through two principal routes [5].

The first route employs carbodiimide-mediated coupling: N-phenylacetyl-L-proline (prepared by acylation of L-proline with phenylacetyl chloride or by carbodiimide coupling of phenylacetic acid with L-proline) is coupled with glycine ethyl ester using 1,3-dicyclohexylcarbodiimide (DCC) with 4-dimethylaminopyridine (DMAP) catalysis. The reaction is typically conducted in a tetrahydrofuran-dichloromethane mixed solvent system at 0 to 5 degrees Celsius, followed by warming to room temperature and stirring for 24 to 48 hours. The product is purified by filtration of the dicyclohexylurea byproduct, solvent evaporation, and recrystallization from ethanol.

The second route employs mixed anhydride coupling: N-phenylacetyl-L-proline is activated with isobutyl chloroformate in the presence of N-methylmorpholine in tetrahydrofuran-dichloromethane at 0 to 5 degrees Celsius for 4 hours, followed by addition of glycine ethyl ester and triethylamine. The product is purified by aqueous workup and recrystallization.

Both routes produce noopept in moderate to good yield (typically 60 to 80 percent for the coupling step) and with high enantiomeric purity reflective of the L-proline starting material. Industrial production optimizes the coupling step and the recrystallization for pharmaceutical-grade purity (greater than 99 percent by HPLC). The compound is characterized by nuclear magnetic resonance spectroscopy (^1H , ^{13}C), high-resolution mass spectrometry, infrared spectroscopy, melting point, and optical rotation [6].

2. Abstract

Noopept (GVS-111; omberacetam; N-phenylacetyl-L-prolylglycine ethyl ester) is a synthetic dipeptide nootropic and neuroprotectant developed at the V.V. Zakusov Research Institute of Pharmacology of the Russian Academy of Medical Sciences in the mid-1990s by Gudasheva, Ostrovskaya, and Seredenin [1, 2]. The compound was designed as a dipeptide analog of piracetam using a drug-based peptide design methodology that maps the pyrrolidone pharmacophore of piracetam onto the prolyl-glycine beta-turn motif [3, 4]. The design strategy was motivated by the observation that short peptides incorporating the structural features of known psychotropic agents could retain or exceed the pharmacological activity of the parent drug while gaining the metabolic and receptor-selectivity advantages of peptide-based ligands.

The principal pharmacological activities of noopept include positive allosteric modulation of AMPA-subtype ionotropic glutamate receptors, modulation of NMDA receptor expression and function, chronic upregulation of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) expression in hippocampal and cortical neurons, activation of hypoxia-inducible factor 1 (HIF-1), and direct neuroprotection against amyloid-beta toxicity, glutamate excitotoxicity, oxidative stress, and ischemic injury [7, 8, 9, 10, 11]. The multifactorial mechanism operates through both the parent compound and the principal active metabolite cycloprolylglycine (CPG), an endogenous brain neuropeptide that is also detectable in human cerebrospinal fluid [12].

Noopept is approved in the Russian Federation (2006) for the treatment of cognitive disorders of vascular and traumatic origin at oral doses of 10 to 30 mg per day, administered in two divided doses for courses of 1.5 to 3 months [13]. These doses are approximately 1000-fold lower by mass than the effective doses of piracetam (1200 to 4800 mg per day), its structural prototype. The compound is not approved by the United States Food and Drug Administration, the European Medicines Agency, or other major Western regulatory authorities. It is available internationally as a research-grade chemical and as an unregulated supplement.

The clinical evidence base is dominated by Russian-language publications. The principal English-language clinical study is the Neznamov and Teleshova (2009) comparative trial of noopept versus piracetam in 53 patients with mild cognitive disorders of vascular and traumatic origin, which demonstrated comparable cognitive efficacy over 56 days with fewer adverse events in the noopept arm [14]. Preclinical evidence is more extensive, encompassing rodent models of ischemic stroke, traumatic brain injury, Alzheimer's disease (amyloid-beta infusion, streptozotocin, and scopolamine models), and age-related cognitive decline [2, 7, 15, 16].

The compound is well tolerated at recommended doses. The principal adverse events (sleep disturbance, irritability, blood pressure elevation) occur at low incidence and resolve with dose reduction. No serious adverse events have been reported in published clinical studies. Long-term safety data beyond 56 days are not available.

3. Discovery and Development History

3.1 Origin and design rationale

Noopept was conceived at the V.V. Zakusov Research Institute of Pharmacology (Russian Academy of Medical Sciences, Moscow) in the early 1990s as part of a systematic program to develop peptide-based analogs of classical nootropic drugs [3, 4]. The program, led by Tatyana Gudasheva and colleagues, was founded on a drug-based peptide design technology that proceeds from the three-dimensional structure of a known non-peptide psychotropic drug (in this case, piracetam) to a short peptide whose backbone reproduces the spatial arrangement of the pharmacophoric elements of the parent drug, typically corresponding to the central region of a beta-turn.

Piracetam (2-oxo-1-pyrrolidineacetamide) was selected as the structural prototype because of its established nootropic activity, its favorable safety profile, and its simple pyrrolidone pharmacophore. The Gudasheva group hypothesized that the pyrrolidone ring of piracetam could be represented as a prolyl residue in a dipeptide configuration, and that the acetamide side chain could be represented as a glycine residue with appropriate N-terminal and C-terminal modifications. The resulting candidate, N-phenylacetyl-L-prolylglycine ethyl ester, incorporated the L-proline pyrrolidine ring (mapping onto the piracetam pyrrolidone), the glycine ethyl ester (mapping onto the piracetam acetamide), and a phenylacetyl N-terminal cap selected from structure-activity optimization for oral bioavailability and blood-brain barrier penetration [3].

3.2 Preclinical characterization

The first pharmacological characterization of GVS-111 was published by the Zakusov Institute group in the late 1990s and early 2000s. Ostrovskaya, Gudasheva, Voronina, and Seredenin (2002) published the comprehensive preclinical profile in *Eksperimental'naya i Klinicheskaya Farmakologiya*, reporting pronounced nootropic activity in the passive avoidance paradigm, the Morris water maze, and multiple other behavioral assays in rats and mice, with effective doses (0.1 to 1 mg/kg intraperitoneally) approximately three orders of magnitude lower than

piracetam (100 to 300 mg/kg) [1]. The same study reported neuroprotective activity in models of bilateral carotid artery occlusion, middle cerebral artery occlusion, and glutamate-induced neurotoxicity in cortical cultures. Gudasheva, Boyko, Akparov, and Ostrovskaya (1996) had previously reported the oral bioactivity of the compound, establishing that the prolyl-glycine dipeptide retained nootropic activity after oral administration despite the expected susceptibility of peptide bonds to gastrointestinal proteolysis [17].

3.3 Clinical development and registration

Clinical trials of noopept were conducted in the Russian Federation under the regulatory framework of the Russian Ministry of Health. The studies were primarily open-label and comparative, examining the efficacy of noopept (10 to 20 mg per day) against piracetam (1200 to 2400 mg per day) in patients with mild to moderate cognitive impairment of cerebrovascular and post-traumatic origin. Noopept was registered in the Russian Federation in 2006 by JSC LEKKO Pharmaceuticals (a subsidiary of JSC Pharmsynthez) as an oral tablet formulation (10 mg) for the treatment of cognitive disorders associated with organic brain disease of vascular and traumatic etiology [13]. Registration was subsequently extended to several former Soviet states including Belarus and Kazakhstan.

3.4 International status

Noopept has not been submitted for regulatory review to the United States Food and Drug Administration, the European Medicines Agency, Health Canada, the Australian Therapeutic Goods Administration, or the Japanese Pharmaceuticals and Medical Devices Agency. The absence of submission reflects a combination of factors: the Russian clinical evidence base does not meet the International Conference on Harmonisation (ICH) standards for pivotal registration in these jurisdictions; the compound is off-patent; and commercial incentive for the substantial investment required for ICH-compliant registration trials has been lacking. The compound is available internationally through chemical research suppliers and through direct-to-consumer supplement channels.

4. Mechanism of Action

Noopept is a multifactorial nootropic and neuroprotectant. Its mechanism of action operates through the parent compound and through its principal active metabolite cycloprolylglycine, with contributions from acute receptor-level effects and from chronic transcriptional regulation of neurotrophic and neuroprotective gene expression.

4.1 AMPA receptor positive allosteric modulation

The AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor is a tetrameric ionotropic glutamate receptor that mediates the majority of fast excitatory neurotransmission in the central nervous system. AMPA receptors are critical substrates for synaptic plasticity, long-term potentiation (LTP), and memory formation.

Noopept and its metabolite cycloprolylglycine function as positive allosteric modulators of AMPA receptors, increasing the sensitivity of the receptor to glutamate without direct agonist binding at the glutamate recognition site [8, 18]. This mechanism is pharmacologically analogous to the ampakine class of AMPA receptor modulators (CX516, CX717, farampator) and is distinct from the direct AMPA agonist mechanism. The positive allosteric modulation slows desensitization and deactivation kinetics, increasing the amplitude and duration of AMPA receptor-mediated excitatory postsynaptic currents. The functional consequence is facilitation of glutamatergic neurotransmission in hippocampal and cortical circuits without the seizure risk associated with direct AMPA agonism.

Bhatt et al. (2013) demonstrated that the AMPA receptor modulation of noopept can be blocked by the AMPA antagonist NBQX, confirming that the procognitive effect in behavioral paradigms is at least partially dependent on AMPA receptor function [18]. The contribution of the cycloprolylglycine metabolite to this mechanism has been confirmed independently; CPG itself modulates AMPA receptor function and produces procognitive effects in behavioral assays [12].

4.2 NMDA receptor modulation

The NMDA (N-methyl-D-aspartate) receptor is a voltage-gated, ligand-gated ionotropic glutamate receptor that serves as the coincidence detector underlying Hebbian synaptic plasticity and long-term potentiation. Noopept modulates NMDA receptor function through multiple mechanisms: the compound influences the expression levels of NMDA receptor subunits (NR1, NR2A, NR2B) in hippocampal and cortical regions on chronic administration, and there is evidence from electrophysiological studies of direct modulation of NMDA receptor-mediated currents [2, 19].

Vorobyov et al. (2011) characterized the EEG effects of chronic noopept administration in awake rats and reported changes in cortical spectral power consistent with glutamatergic modulation, with the NMDA receptor contribution confirmed by selective antagonist studies [19]. The NMDA receptor modulation is not antagonistic (unlike memantine or ketamine) but facilitatory, consistent with enhancement rather than blockade of synaptic plasticity mechanisms.

4.3 Neurotrophic factor upregulation

The chronic upregulation of neurotrophic factor expression is a distinctive feature of noopept pharmacology that differentiates it from classical racetam nootropics.

Gudasheva and colleagues (2009) demonstrated that chronic (28-day) administration of noopept to rats increased BDNF mRNA and protein levels in the hippocampus and increased both NGF and BDNF expression in cortical and hippocampal regions [9]. The time course of the neurotrophic response (requiring days to weeks of administration) is consistent with transcriptional regulation rather than acute receptor-level effects and provides a mechanistic basis for the observation that the full cognitive benefit of noopept develops over days to weeks of continuous dosing rather than appearing immediately on acute administration.

NGF and BDNF are members of the neurotrophin family that promote neuronal survival, axonal and dendritic growth, synaptic plasticity, and long-term potentiation through activation of the TrkA (for NGF) and TrkB (for BDNF) receptor tyrosine kinases. The downstream signaling cascades include activation of phosphoinositide 3-kinase/Akt, mitogen-activated protein kinase/ERK, and phospholipase C-gamma pathways. The neurotrophic mechanism of noopept is therefore a substrate for both procognitive and neuroprotective effects and is likely the principal mechanism for the sustained benefit observed in chronic dosing regimens.

4.4 HIF-1 transcription factor activation

Noopept activates hypoxia-inducible factor 1 (HIF-1) through inhibition of HIF-1 prolyl hydroxylase, the oxygen-sensing enzyme that targets the HIF-1 α subunit for proteasomal degradation under normoxic conditions [10]. Activation of HIF-1 under normoxic conditions (pharmacological pseudohypoxia) induces the expression of a suite of HIF-1 target genes involved in glucose metabolism (glycolytic enzymes, glucose transporters), erythropoiesis (erythropoietin), angiogenesis (vascular endothelial growth factor), iron homeostasis, and cell survival signaling.

Vakhitova et al. (2020) demonstrated that noopept increased both the basal DNA-binding activity of HIF-1 and the activity induced by hypoxia mimetics (cobalt chloride, deferoxamine) in neuronal cell culture models, and that the mechanism involved stabilization of the HIF-1 α subunit through prolyl hydroxylase inhibition [10]. The HIF-1 activation provides a mechanistic basis for the neuroprotective activity of noopept in ischemic and hypoxic brain injury models, where increased glycolytic capacity, improved glucose utilization, and enhanced cell survival signaling counteract the metabolic consequences of oxygen deprivation.

4.5 Neuroprotection against amyloid-beta toxicity and tau hyperphosphorylation

Ostrovskaya et al. (2014) characterized the neuroprotective effect of noopept in an Alzheimer's disease-related cellular model (PC12 cells treated with amyloid-beta 25-35 peptide) and reported that noopept pretreatment improved cell viability, reduced the number of early and late apoptotic cells, reduced intracellular reactive oxygen species and calcium levels, enhanced mitochondrial membrane potential, attenuated tau hyperphosphorylation at Ser396, and restored neurite outgrowth [11]. The mechanism of protection involved inhibition of the mitochondrial apoptotic pathway (suppression of cytochrome c release, reduction of caspase-3 activation) and antioxidant effects (reduction of reactive oxygen species generation, prevention of calcium overload).

Ostrovskaya et al. (2007) had previously demonstrated in an *in vivo* Alzheimer's disease model (intracerebral infusion of amyloid-beta 25-35 in rats) that chronic noopept administration restored spatial memory and increased immunoreactivity to amyloid, suggesting promotion of amyloid clearance or processing [15].

4.6 Cholinergic facilitation

There is limited evidence of modest cholinergic facilitation by noopept, likely indirect rather than direct. The compound does not inhibit acetylcholinesterase and does not bind muscarinic or nicotinic acetylcholine receptors at pharmacologically relevant concentrations. However, the BDNF and NGF upregulation in the basal forebrain cholinergic system (a primary target of NGF trophic support) may produce secondary enhancement of cholinergic neurotransmission through improved survival and function of cholinergic projection neurons [9].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Noopept is rapidly absorbed from the gastrointestinal tract after oral administration, with time to peak plasma concentration of approximately 15 to 20 minutes in rats and estimated similarly rapid absorption in humans [20]. Oral bioavailability is approximately 10 percent relative to intraperitoneal administration, reflecting extensive first-pass metabolism by gastrointestinal and hepatic peptidases and esterases [20]. Despite the low oral bioavailability of the parent compound, the pharmacological effect after oral dosing is substantial, consistent with the bioactivity of the cycloprolylglycine metabolite generated during first-pass metabolism and with the high potency of the parent compound at its target concentrations.

5.2 Distribution

The volume of distribution has not been fully characterized in humans. In rodent studies, noopept crosses the blood-brain barrier, with brain concentrations detectable within minutes of systemic administration [20]. The compound distributes to cortical and hippocampal regions, consistent with its pharmacological target distribution. Plasma protein binding has not been comprehensively reported; the relatively hydrophobic character of the phenylacetyl cap and the ethyl ester suggests moderate protein binding.

5.3 Metabolism

The principal metabolic pathway is peptidase-mediated hydrolysis. The parent compound undergoes sequential cleavage: ester hydrolysis of the C-terminal ethyl ester yields N-phenylacetyl-L-prolylglycine (the free acid), followed by cyclization to yield cycloprolylglycine (cyclo-L-prolylglycine, CPG), the principal circulating and brain metabolite [12, 20]. CPG is an endogenous brain dipeptide also present in

normal human cerebrospinal fluid, and it possesses independent nootropic and neuroprotective activity through AMPA receptor modulation and TrkB receptor-dependent mechanisms.

Importantly, the metabolism of noopept does not appear to involve significant cytochrome P450-mediated oxidation. The biotransformation is predominantly through peptidases and esterases, and the compound does not inhibit or induce major CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) at pharmacologically relevant concentrations [2]. This metabolic profile substantially reduces the potential for cytochrome P450-mediated drug-drug interactions compared to compounds with hepatic oxidative metabolism.

Boiko et al. (2018) characterized the pharmacokinetics of noopept and cyclopropylglycine in rats, reporting that CPG exhibited a substantially longer plasma half-life than the parent compound and appeared in brain tissue at pharmacologically relevant concentrations following oral noopept administration [20].

5.4 Elimination

The parent compound is eliminated rapidly from plasma (plasma half-life estimated at approximately 15 to 25 minutes in rats for the parent compound). The cyclopropylglycine metabolite has a longer plasma residence (half-life approximately 1 to 2 hours), and the pharmacological effect persists for 3 to 6 hours after oral dosing, substantially longer than the plasma residence of either the parent compound or CPG [20]. This temporal dissociation between plasma pharmacokinetics and pharmacological effect is consistent with the transcriptional and neurotrophic mechanisms (which persist beyond receptor occupancy) and with tissue accumulation of the metabolite.

Elimination of the metabolites is predominantly renal, as water-soluble peptide fragments and amino acids. A comprehensive human mass-balance study has not been published.

5.5 Routes of administration

Three principal routes are used clinically and in research:

Oral: The registered route. Tablets of 10 mg are administered twice daily (morning and midday) for total daily doses of 10 to 20 mg, with some protocols employing 30 mg per day in three divided doses. Oral administration is convenient but yields the lowest bioavailability of the parent compound (approximately 10 percent).

Sublingual: Used in supplement contexts to bypass first-pass metabolism and increase bioavailability. Sublingual dosing reduces the first-pass hydrolysis of the parent compound by gastrointestinal peptidases, potentially increasing systemic exposure to the intact parent molecule. Formal bioavailability comparisons with oral administration have not been published in peer-reviewed literature.

Intranasal: Used in some research contexts for rapid CNS delivery. Intranasal administration bypasses gastrointestinal first-pass metabolism and may permit direct olfactory nerve-mediated delivery to the central nervous system. Formal pharmacokinetic characterization of intranasal noopept has not been published.

5.6 Special populations

Dedicated pharmacokinetic studies in renal impairment, hepatic impairment, pediatric, and geriatric populations have not been published. Given the peptidase-dependent (rather than CYP-dependent) metabolism, hepatic impairment would be expected to have a smaller effect on noopept pharmacokinetics than on compounds with predominantly hepatic oxidative metabolism. The compound is not recommended for use in pregnancy or lactation (insufficient safety data). Pediatric use has not been studied.

6. Preclinical Pharmacology

6.1 Cognitive enhancement in rodent models

Noopept has demonstrated procognitive activity in a broad range of rodent behavioral paradigms. In the passive avoidance test, the compound improved learning and memory consolidation at intraperitoneal doses of 0.1 to 1 mg/kg, with efficacy comparable to or exceeding piracetam at 100 to 300 mg/kg [1]. In the Morris water maze, chronic noopept administration improved spatial learning and memory in both young and aged rats [2]. In the novel object recognition paradigm, acute and chronic noopept administration improved recognition memory.

The procognitive effect has been demonstrated in pharmacological deficit models (scopolamine-induced amnesia, ethanol-induced amnesia, electroconvulsive shock amnesia) and in lesion models (bilateral common carotid artery occlusion, middle cerebral artery occlusion). In each model, noopept restored cognitive performance toward or to the level of intact controls at doses 100- to 1000-fold lower by mass than piracetam [1, 2].

6.2 Neuroprotection in ischemic models

Noopept provided neuroprotection in multiple models of cerebral ischemia. In the bilateral common carotid artery occlusion model in rats, noopept reduced infarct volume and improved neurological scores when administered either before or after the ischemic insult [1]. In cortical neuron cultures subjected to oxygen-glucose deprivation, noopept improved cell survival at micromolar concentrations [21]. Pealsman et al. (2003) demonstrated that GVS-111 prevented oxidative damage and apoptosis in normal and Down's syndrome human cortical neurons in vitro, extending the neuroprotective profile to human cellular models [22].

The neuroprotective mechanism involves multiple parallel pathways: antioxidant activity (reduction of reactive oxygen species), anti-excitotoxic effects (modulation of glutamate receptor overactivation), anti-apoptotic effects (suppression of the mitochondrial apoptotic cascade), calcium homeostasis (prevention of calcium overload), and HIF-1 activation (improved glucose metabolism and cell survival signaling) [10, 11, 21].

6.3 Alzheimer's disease models

In the intracerebral amyloid-beta 25-35 infusion model in rats, chronic noopept administration restored spatial memory in the Morris water maze and increased immunoreactivity to amyloid in hippocampal tissue [15]. In the Alzheimer's disease cellular model (PC12 cells exposed to amyloid-beta 25-35), noopept attenuated apoptosis, reduced tau hyperphosphorylation at Ser396, improved mitochondrial membrane potential, and restored neurite outgrowth [11]. In the streptozotocin intracerebroventricular injection model (a model of sporadic Alzheimer's disease), noopept ameliorated cognitive deficits and reduced markers of oxidative stress [16].

The cycloprolylglycine metabolite has also demonstrated neuroprotective activity in Alzheimer's disease models. In the intracerebral amyloid-beta infusion model, CPG reduced hippocampal cell death, increased BDNF mRNA expression, increased expression of the anti-inflammatory cytokine IL-4, and reduced expression of the pro-inflammatory cytokine IL-6 [12].

6.4 Anti-inflammatory activity

Noopept and cycloprolylglycine modulate neuroinflammatory signaling. The reduction of IL-6 and increase of IL-4 by CPG in the amyloid-beta infusion model suggest a shift from pro-inflammatory to anti-inflammatory cytokine balance [12]. The HIF-1 activation by noopept may contribute to anti-inflammatory effects through modulation of NF-kappaB signaling. Direct characterization of noopept effects on microglial activation and on peripheral inflammatory models is limited.

6.5 Anxiolytic activity

Noopept has been reported to possess anxiolytic-like effects in rodent models, including the elevated plus maze and light-dark box paradigms [2]. The anxiolytic effect is modest and is most pronounced in chronically stressed or anxiety-prone animal strains. The mechanism likely involves the neurotrophic and glutamatergic modulatory effects rather than direct GABAergic or serotonergic activity.

7. Clinical Evidence Base

7.1 Comparative trial in cognitive disorders of vascular and traumatic origin

The principal English-language clinical study is the Neznamov and Teleshova (2009) open-label comparative trial of noopept and piracetam in 53 patients with mild cognitive disorders of organic brain diseases of vascular and traumatic origin [14]. Patients were randomized to noopept 20 mg per day (10 mg morning, 10 mg afternoon; n = 31) or piracetam 1200 mg per day (400 mg three times daily; n = 22) for 56 days. Both treatment groups showed statistically significant improvement from baseline on cognitive testing batteries including memory, attention, and executive function measures. The magnitude of cognitive improvement was comparable between groups despite the approximately 60-fold difference in daily dose by mass. Adverse events were reported at a 1.8-fold lower incidence in the noopept arm compared to piracetam.

Reported adverse events in the noopept group included sleep disturbances (5 of 31 patients, 16.1 percent), irritability (3 of 31 patients, 9.7 percent), and blood pressure elevation (7 of 31 patients, 22.6 percent). The adverse events were described as mild and did not require treatment discontinuation. Electroencephalographic analysis showed improvements in cortical bioelectrical activity in both treatment groups.

7.2 Treatment of cognitive impairment after stroke

Amelin et al. (2011) reported on the use of noopept 20 mg per day for 2 months in patients with post-stroke cognitive impairment, demonstrating statistically significant improvement on the Mini-Mental State Examination and other cognitive measures, with acceptable tolerability [23]. The compound was reported to improve both cognitive and emotional parameters in the post-stroke rehabilitation context.

7.3 Russian-language clinical literature

The broader clinical evidence base for noopept is predominantly Russian-language and includes additional open-label and comparative studies in patients with cognitive impairment of vascular, traumatic, and neurodegenerative origin. Seredenin and Voronina (2012) and colleagues have published multiple clinical reports documenting efficacy and safety across various patient populations [13]. The studies generally report cognitive improvement on standardized testing batteries, acceptable tolerability, and low adverse-event incidence. However, the methodological standards (open-label designs, small sample sizes, absence of placebo arms in some studies, limited blinding) do not meet the International Conference on Harmonisation (ICH) standards required for regulatory submissions in Western jurisdictions.

7.4 Limitations of the clinical evidence base

The clinical evidence for noopept is limited by several factors: the predominance of Russian-language publications with restricted international peer review; the absence of large-scale, multicenter, double-blind, placebo-controlled registration trials meeting ICH standards; the absence of published long-term safety data beyond 56 days; the absence of dedicated pharmacokinetic studies in human subjects characterizing the parent compound and metabolite concentrations; and the absence of studies in Western patient populations with standardized cognitive assessment batteries (ADAS-Cog, MATRICS, CANTAB) commonly used in Western regulatory submissions.

8. Sourcing and Quality Verification

Research-grade noopept is available from multiple international chemical suppliers including Cayman Chemical, Sigma-Aldrich (Merck), MedChemExpress, Tocris, Santa Cruz Biotechnology, APExBIO, BocSci, and others. Supply is in milligram to gram quantities as the free base (the ethyl ester). Pricing is moderate, in the range of \$30 to \$150 per gram at the time of monograph preparation, varying by supplier and quantity.

Pharmaceutical-grade noopept (Noopept brand, 10 mg oral tablets) is manufactured by JSC LEKKO Pharmaceuticals in the Russian Federation and is available through Russian pharmacies and through international pharmacy intermediaries. The pharmaceutical-grade material is the highest quality source for research where regulatory traceability is operationally important.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (319.1652 for the protonated molecule $[M+H]^+$ or 318.1580 monoisotopic)
- Optical rotation measurement ($[\alpha]_D$ -115 to -125 degrees, $c = 0.5$ in chloroform) or chiral HPLC to confirm enantiomeric integrity of the L-proline stereocenter
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer titration or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography (common synthesis solvents: tetrahydrofuran, dichloromethane, ethanol, ethyl acetate)

Third-party analytical confirmation (Janoshik Analytical, Anabolic Lab, or equivalent) is recommended for any lot intended for biological studies where dose-response precision is critical. The noopept research chemical market is well estab-

lished but is also a target for adulteration in the consumer supplement space; analytical confirmation is particularly important for material obtained through unregulated supplement channels.

9. Reconstitution and Handling

Noopept is supplied as a white to off-white crystalline powder. The compound is soluble in dimethyl sulfoxide (DMSO) at concentrations up to 25 mg/mL and is sparingly soluble in water. For in vitro research applications, stock solutions are typically prepared at 10 to 50 mM in DMSO and diluted into culture medium to achieve final concentrations in the micromolar range. The final DMSO concentration in culture medium should be maintained below 0.1 percent (v/v) to avoid solvent toxicity.

For in vivo research, the compound can be dissolved in physiological saline with gentle warming and brief sonication; the addition of a small percentage of DMSO (less than 5 percent) or polyethylene glycol 400 may be required for concentrations above 1 mg/mL in aqueous solution. For oral gavage studies in rodents, suspension in 0.5 percent carboxymethylcellulose is an alternative.

Storage of the dry powder at 2 to 8 degrees Celsius is recommended; the compound is stable at room temperature in dry conditions for extended periods but refrigerated storage extends shelf life. Solutions in DMSO should be aliquoted for single-use and stored at -20 degrees Celsius; stability of DMSO stock solutions is reported at up to 2 months at -20 degrees Celsius. Aqueous solutions are less stable due to hydrolysis of the ethyl ester bond and should be prepared fresh on the day of use or stored frozen for no more than 7 days.

Light protection is not strictly required but is reasonable practice for long-term storage. The compound is not hygroscopic but should be stored in sealed containers to prevent exposure to atmospheric moisture.

10. Stack Interactions and Combinations

Noopept is commonly used in combination (stacked) with other nootropic compounds in both research and supplement contexts. The pharmacokinetic profile of noopept (peptidase-mediated metabolism, absence of significant CYP450 involvement) reduces the potential for metabolic drug-drug interactions compared to compounds with hepatic oxidative metabolism.

Choline sources (alpha-GPC, citicoline, choline bitartrate): The combination of noopept with supplemental choline is widely reported in the nootropic community and has a theoretical basis in the cholinergic facilitation component of noopept pharmacology. The BDNF and NGF upregulation in the basal forebrain cholinergic system may increase cholinergic neurotransmission demands; supplemental choline ensures adequate substrate for acetylcholine synthesis and may reduce the incidence of headache reported by some individuals on noopept monotherapy [24]. Formal controlled studies of the noopept-choline combination have not been published.

Racetam nootropics (piracetam, aniracetam, oxiracetam, phenylpiracetam): Combination of noopept with racetams is common in nootropic practice. The mechanisms are partially overlapping (AMPA receptor modulation, glutamatergic facilitation) and partially complementary (racetams increase membrane fluidity and cerebral blood flow; noopept provides neurotrophic upregulation). Additive or synergistic effects on cognitive endpoints have been reported anecdotally but have not been formally characterized in controlled studies. The combination may increase cholinergic demand and should be paired with a choline source. Investigators should exercise caution with high-dose combinations to avoid excessive glutamatergic stimulation.

Acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine): The theoretical basis for combination exists (complementary mechanisms of cholinergic facilitation and glutamatergic modulation), but no formal interaction studies have been published. Additive cholinergic effects should be anticipated.

Anxiolytics and sedatives: Noopept possesses modest anxiolytic activity; combination with GABAergic anxiolytics (benzodiazepines, phenibut) may produce additive central nervous system depression. Combination with alcohol is not recommended owing to additive sedation.

Psychostimulants: Combination with amphetamine, methylphenidate, or modafinil introduces the possibility of additive excitatory effects on glutamatergic and catecholaminergic neurotransmission. Formal interaction data are not available; caution is appropriate.

Serotonergic agents: No serotonergic interaction is predicted from the known mechanism of noopept, but the absence of formal interaction studies warrants caution with concurrent serotonin reuptake inhibitors, monoamine oxidase inhibitors, and serotonergic triptans.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported in clinical studies at doses of 10 to 30 mg per day are:

- Sleep disturbance (insomnia, vivid dreams): approximately 16 percent in the Neznamov 2009 study (5 of 31 patients)
- Blood pressure elevation: approximately 23 percent (7 of 31 patients), generally transient and clinically insignificant
- Irritability: approximately 10 percent (3 of 31 patients)
- Headache: reported at low incidence in supplement-user reports; frequency not precisely quantified in clinical studies
- Gastrointestinal discomfort: rare at recommended doses

These adverse events are described as mild, dose-dependent, and resolving with dose reduction or treatment discontinuation. The overall adverse-event incidence was 1.8-fold lower than that observed with piracetam 1200 mg per day in the head-to-head comparative trial [14].

11.2 Serious adverse events

No serious adverse events have been reported in published clinical studies of noopept at doses up to 30 mg per day for up to 56 days. The compound has not been associated with hepatotoxicity, nephrotoxicity, hematological toxicity, or cardiac arrhythmia in published reports.

11.3 Preclinical toxicology

The acute oral LD₅₀ in rats is greater than 2000 mg/kg, representing a safety margin of approximately 100-fold or greater above the therapeutic dose range [2]. No carcinogenicity, mutagenicity, or teratogenicity has been reported in standard preclinical toxicology batteries. The compound does not stimulate cell proliferation, as

demonstrated by Zhuravin et al. (2019) in a study specifically addressing the question of whether the neuroprotective and neurotrophic properties of noopept might promote neoplastic growth [25].

11.4 Limitations of safety data

The principal limitation of the safety database is the absence of long-term (greater than 56 days) controlled safety data in humans. The compound is used in clinical practice in the Russian Federation in courses of 1.5 to 3 months with intervals between courses, but systematic long-term safety monitoring data have not been published in peer-reviewed literature. The absence of dedicated human pharmacokinetic studies (quantifying parent compound and metabolite plasma concentrations) represents a further limitation for safety assessment.

Psychiatric adverse effects have been reported in isolated case reports associated with nootropic use. Brem and Bhatt (2015) published a case series of four patients experiencing psychiatric adverse events (mania, psychosis) associated with nootropic supplement use; while the cases involved multiple compounds simultaneously, they highlight the need for caution in individuals with pre-existing psychiatric conditions [26].

11.5 Pregnancy and lactation

No human pregnancy or lactation data are available. Preclinical teratogenicity studies have not demonstrated developmental toxicity at standard multiples of the therapeutic dose. Use in pregnancy and lactation is not recommended owing to insufficient safety data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five nootropic or neuroprotective compounds against noopept, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected on the basis of overlapping mechanism, clinical use in cognitive disorders, or structural relationship to noopept.

12.1 Piracetam

Mechanism: Piracetam (2-oxo-1-pyrrolidineacetamide) is the prototype racetam nootropic. It modulates AMPA receptor function, enhances membrane fluidity, increases cerebral blood flow, and modulates neurotransmitter release without direct agonist or antagonist activity at major receptor systems [27]. It does not upregulate NGF or BDNF.

Novelty: Low. Piracetam was synthesized in 1964 and is the founding member of the racetam class. The mechanism has been studied for over 50 years.

Effect size: Modest. Clinical trials in age-related cognitive decline and dementia have produced small effect sizes that have not consistently supported registration in major Western jurisdictions, though the compound is registered in several European and Asian countries. The Neznamov 2009 comparative trial reported comparable cognitive improvement between noopept 20 mg per day and piracetam 1200 mg per day, but at a 60-fold greater mass dose for piracetam [14].

Promising potential: Low for new indications. Piracetam is a mature compound with established clinical positioning and no active clinical development program for novel indications.

Side-effect profile: Favorable. Piracetam is well tolerated at doses of 1200 to 4800 mg per day. Adverse events (gastrointestinal discomfort, headache, insomnia, weight gain) are mild and uncommon. The Neznamov 2009 trial reported 1.8-fold more adverse events with piracetam than with noopept.

Overall validation: Moderate. Piracetam has the most extensive clinical evidence base of any nootropic compound, with hundreds of published clinical studies. However, the effect sizes are modest, and the compound has not achieved FDA approval.

Comparison to noopept: Noopept was designed as a peptide analog of piracetam and shares the AMPA receptor modulatory mechanism. Noopept is approximately 1000-fold more potent by mass, produces neurotrophic upregulation that piracetam does not, and has a more favorable adverse-event profile at therapeutic doses. Piracetam has the advantage of a vastly larger clinical evidence base and decades of clinical use.

12.2 Aniracetam

Mechanism: Aniracetam (1-p-anisoyl-2-pyrrolidinone) is a fat-soluble racetam with AMPA receptor positive allosteric modulation (ampakine activity), group I metabotropic glutamate receptor modulation, and anxiolytic effects mediated through dopaminergic and serotonergic modulation [28]. It does not upregulate NGF or BDNF.

Novelty: Low to moderate. The ampakine mechanism and the anxiolytic-nootropic combination profile are differentiated within the racetam class.

Effect size: Modest in clinical studies. Aniracetam has been studied in Alzheimer's disease and vascular dementia in Japan and Europe, with small positive effects on cognitive and global function measures. The compound is registered in Japan and several European countries for cognitive impairment in the elderly.

Promising potential: Low. The compound is a mature generic with no active clinical development program.

Side-effect profile: Favorable. Well tolerated at doses of 750 to 1500 mg per day. Principal adverse events are mild gastrointestinal discomfort and headache.

Overall validation: Moderate. Registered in several jurisdictions; clinical evidence base is of moderate size.

Comparison to noopept: Aniracetam shares the AMPA receptor modulatory mechanism with noopept but lacks the neurotrophic upregulation and HIF-1 activation. Aniracetam has stronger anxiolytic effects through serotonergic and dopamin-

ergic modulation. Noopept has greater potency and a broader neuroprotective mechanism. Aniracetam has a more established regulatory and clinical record in some jurisdictions.

12.3 Phenylpiracetam (Fonturacetam)

Mechanism: Phenylpiracetam (4-phenyl-2-pyrrolidone-1-yl acetamide) is a phenyl-substituted piracetam analog with nootropic, psychostimulant, and anticonvulsant activity [29]. The compound modulates glutamate and acetylcholine neurotransmission, enhances physical performance and cold tolerance, and has reported anti-amnestic and anxiolytic effects. Unlike noopept, it has a psychostimulant component sufficient to place it on the World Anti-Doping Agency prohibited list.

Novelty: Moderate. The combination of nootropic, psychostimulant, and physical performance enhancement is distinctive within the racetam class.

Effect size: Moderate in preclinical models of cognitive impairment and physical performance. Human clinical data are limited and predominantly Russian-language. Cognitive improvement has been reported in patients with chronic cerebrovascular insufficiency.

Promising potential: Low. The compound is a mature generic, registered in the Russian Federation. Development for Western markets has not been pursued.

Side-effect profile: Moderate. The psychostimulant component produces insomnia and agitation at higher doses, and the compound is banned by WADA for competition use. Tolerability is otherwise acceptable.

Overall validation: Low to moderate. Clinical evidence base is small and concentrated in Russian-language literature.

Comparison to noopept: Phenylpiracetam has stronger psychostimulant and physical performance effects than noopept. Noopept has stronger neuroprotective and neurotrophic effects. Noopept lacks the WADA-prohibited stimulant activity of phenylpiracetam. The two compounds target overlapping but distinct neurochemical substrates.

12.4 Semax

Mechanism: Semax (Met-Glu-His-Phe-Pro-Gly-Pro) is a synthetic heptapeptide analog of the adrenocorticotrophic hormone (ACTH) fragment 4-10, developed at the Institute of Molecular Genetics of the Russian Academy of Sciences [30]. It lacks adrenocorticotrophic and steroidogenic activity but produces nootropic, neuroprotective, and neurotrophic effects through modulation of BDNF and NGF expression, activation of dopaminergic and serotonergic systems, and melanocortin receptor modulation.

Novelty: Moderate to high. The melanocortin-derived peptide nootropic mechanism is distinct from the racetam-derived and glutamatergic mechanisms of noopept.

Effect size: Moderate in preclinical models; clinical evidence in Russia supports efficacy in cerebrovascular cognitive impairment and optic nerve atrophy. Published clinical trials are predominantly Russian-language.

Promising potential: Moderate. The compound is registered in the Russian Federation for cognitive impairment and is available through research and supplement channels.

Side-effect profile: Favorable. The compound is well tolerated with minimal reported adverse events. Administration is typically intranasal, which avoids gastrointestinal adverse events.

Overall validation: Moderate. Clinical evidence is of moderate size but concentrated in Russian-language literature.

Comparison to noopept: Both noopept and semax upregulate BDNF and NGF expression, but through different molecular mechanisms (glutamatergic and HIF-1 modulation for noopept; melanocortin receptor-dependent signaling for semax). Semax is a larger peptide requiring intranasal administration (poor oral bioavailability), whereas noopept is orally bioactive. Both compounds share the limitation of a predominantly Russian-language clinical evidence base. The mechanisms are complementary, and concurrent use has been reported in nootropic practice, though formal combination studies have not been published.

12.5 Cerebrolysin

Mechanism: Cerebrolysin is a mixture of low-molecular-weight neuropeptides and free amino acids derived from porcine brain tissue by standardized enzymatic proteolysis [31]. The active constituents include fragments with neurotrophic factor-like activity that activate TrkB and p75NTR receptors and mimic the downstream effects of BDNF and NGF. The compound modulates glutamate-mediated excitotoxicity, reduces tau hyperphosphorylation, promotes neurogenesis, and provides neuroprotection in ischemic and neurodegenerative models.

Novelty: Low. The compound is a complex biological mixture rather than a defined chemical entity; it has been in clinical use since the 1970s.

Effect size: Moderate. Multiple randomized controlled trials, including Western-standard ICH-compliant studies, have demonstrated modest but statistically significant cognitive improvement in Alzheimer's disease and vascular dementia. A Cochrane review (2013) concluded that cerebrolysin had positive effects on global clinical impression in Alzheimer's disease, though with methodological limitations [32].

Promising potential: Moderate. The compound is registered in over 40 countries (not including the United States) and has ongoing clinical development.

Side-effect profile: Generally favorable. The compound requires parenteral (intravenous or intramuscular) administration, which limits outpatient convenience. Injection-site reactions, headache, and dizziness are the principal adverse events. Rare allergic reactions have been reported.

Overall validation: Moderate to high. The compound has the most extensive clinical evidence base for a neurotrophic agent in Alzheimer's disease and vascular dementia, including large multicenter randomized trials.

Comparison to noopept: Both compounds provide neurotrophic-type neuroprotection, but through fundamentally different approaches: noopept is a defined small molecule that upregulates endogenous neurotrophic factor expression, while cerebrolysin is a complex mixture that directly provides neurotrophic peptide fragments. Noopept has the advantage of oral bioavailability and a defined chemical composition; cerebrolysin has the advantage of a substantially larger and method-

ologically stronger clinical evidence base, including studies meeting Western regulatory standards. Cerebrolysin requires parenteral administration, limiting convenience compared to oral noopept.

12.6 Comparator summary

The five comparators span a range of nootropic mechanisms and clinical development states. **Piracetam** is the structural prototype of noopept and shares the AMPA receptor modulatory mechanism but lacks the neurotrophic upregulation and is approximately 1000-fold less potent by mass. **Aniracetam** adds anxiolytic properties and fat-soluble AMPA receptor modulation but similarly lacks neurotrophic effects. **Phenylpiracetam** adds psychostimulant and physical performance effects but carries WADA prohibition and a weaker neuroprotective profile. **Semax** provides complementary neurotrophic upregulation through a melanocortin-derived peptide mechanism but requires intranasal administration and shares the limitation of a predominantly Russian clinical evidence base. **Cerebrolysin** is the closest mechanistic comparator for neurotrophic neuroprotection and has the strongest clinical evidence base but requires parenteral administration and is a complex biological rather than a defined chemical entity.

Noopept occupies a distinctive position in this comparator landscape as the only compound that combines defined small-molecule oral bioavailability, AMPA receptor positive allosteric modulation, neurotrophic factor upregulation (NGF and BDNF), HIF-1 activation, and direct amyloid-beta neuroprotection in a single agent at milligram-range doses. Its principal limitations are the modest size and methodological quality of the clinical evidence base (predominantly Russian-language, open-label, small-sample designs) and the absence of regulatory approval in Western jurisdictions. Investigators considering noopept for cognitive or neuroprotective research should weigh the compelling preclinical mechanism and favorable safety signal against the limited clinical validation, and should note that the closest clinical comparator for neurotrophic neuroprotection (cerebrolysin) has achieved a substantially stronger clinical evidence base, albeit with the disadvantage of parenteral-only administration.

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