

RESEARCH MONOGRAPH . COMPOUND PROFILE

Hopantenic acid

A synthetic homolog of pantothenic acid in which beta-alanine is replaced by gamma-aminobutyric acid, developed in the Soviet Union and Japan as a nootropic and neuroprotective agent with registered indications across pediatric and adult neurology in the Russian Federation.

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ABSTRACT

Hopantenic acid (homopantothenic acid, D-homopantothenic acid, N-pantoyl-GABA) is a synthetic structural analog of pantothenic acid (vitamin B5) in which the beta-alanine moiety is replaced by gamma-aminobutyric acid (GABA), producing a hybrid molecule that combines GABAergic pharmacology with pantothenate-related metabolic activity and the capacity to cross the blood-brain barrier, a property that free GABA lacks. The compound was first synthesized in the 1950s in Japan, entered clinical use as the calcium salt (calcium hopantenate) in Japan in 1978 and in the Soviet Union in 1977, and is registered in the Russian Federation under the brand names Pantogam and Pantocalcin for a broad range of neurological, psychiatric, and developmental indications in children and adults, including cognitive impairment of cerebrovascular origin, attention deficit hyperactivity disorder, perinatal encephalopathy, cerebral palsy with hyperkinetic features, epilepsy adjunctive therapy, neurogenic bladder disorders, stuttering, and tic disorders. A racemic formulation (D,L-hopantenic acid, marketed as Pantogam Active) was introduced in Russia in 2008 and exhibits enhanced anxiolytic and anticonvulsant properties attributed to the L-isomer's interaction with GABA-A receptors and dopamine D2 receptors. The compound is not approved by the United States Food and Drug Administration, by the European Medicines Agency, or by any Western regulatory authority. The molecular pharmacology of hopantenic acid is multifaceted. At the neurotransmitter level, the compound acts as a weak agonist at the GABA-B receptor complex, with a cross-reactive potency of approximately 0.2 percent relative to GABA in radioreceptor

assays, and interacts with GABA-A receptors and dopamine D2 receptors at higher concentrations. In parallel, hopantenic acid enhances high-affinity choline transport into cortical and hippocampal synaptosomes and stimulates choline acetyltransferase activity, producing a secondary cholinergic facilitation that is the principal basis for the nootropic and antimentia pharmacology characterized in preclinical studies by Nakahiro et al. (1988) and others [1, 2]. At the metabolic level, the compound is a competitive antagonist of pantothenic acid at the pantothenate kinase step of coenzyme A (CoA) biosynthesis; phosphorylation by pantothenate kinase produces phosphohopantenic acid, which potently inhibits phosphopantothenoylcysteine synthetase and reduces cellular CoA levels [3]. This pantothenic acid antagonism is the molecular basis for the most serious reported adverse effect of the compound: a Reye-like syndrome of acute encephalopathy with hepatic steatosis, hyperammonemia, and hypoglycemia reported in multiple case series in Japan during the 1980s, principally in elderly and pediatric patients on chronic high-dose therapy, and reproduced in dogs by Noda et al. (1991) [4, 5, 6]. The encephalopathy was preventable by concurrent pantothenic acid supplementation, confirming the antagonistic mechanism. Pharmacokinetics following oral administration of the calcium salt are characterized by rapid absorption (time to peak plasma concentration approximately 1.5 hours), moderate oral bioavailability (approximately 64 percent in preclinical models), an elimination half-life of approximately 6.7 hours, and predominantly renal excretion without significant hepatic metabolism [7]. The clinical evidence base for hopantenic acid is dominated by Russian-language publications of variable methodological rigor, with the most robust trial being a

multicenter, double-blind, placebo-controlled study of Pantogam in 100 children with attention deficit hyperactivity disorder, which reported statistically significant improvement on the ADHD-DSM-IV rating scale and sustained attention measures over four months at 30 mg/kg/day [8]. Additional clinical evidence supports the use of the racemic formulation (Pantogam Active) for cognitive and anxiety disorders in patients with arterial hypertension and chronic cerebral ischemia [9, 10]. This monograph reviews the chemistry, synthesis, and stereochemistry of hopantenic acid; the multifaceted mechanism of action spanning GABAergic, cholinergic, and CoA-related pathways; the pharmacokinetic profile; the clinical evidence across registered and investigational indications; the Reye-like encephalopathy safety signal and its mechanistic basis; sourcing and quality verification; reconstitution and handling; stack interactions; and a structured comparative assessment of five alternative nootropic and GABAergic compounds against hopantenic acid on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Hopantenic acid (not assigned a formal INN by the World Health Organization; the name "hopantenic acid" is the accepted common name in English-language pharmacological literature and regulatory databases).

Marketed names: Pantogam (PIQ-Pharma, Russian Federation; the principal branded formulation of R-hopantenic acid calcium salt in tablet and syrup forms), Pantocalcin (Russian Federation; an alternative branded formulation of the calcium salt), Pantogam Active (PIQ-Pharma, Russian Federation; the racemic D,L-hopantenic acid formulation in capsule form, introduced 2008). In Japan, the compound was marketed as calcium hopantenate under several generic designations during the 1970s and 1980s.

Synonyms: Homopantothenic acid, D-homopantothenic acid, N-pantoyl-GABA, pantoyl-GABA, N-(2,4-dihydroxy-3,3-dimethylbutyryl)-4-aminobutyric acid. The abbreviation "HOPA" appears in some pharmacological literature.

Chemical Abstracts Service registry numbers: 18679-90-8 (free acid, R-configuration), 17097-76-6 (calcium salt), 49831-65-4 (racemic free acid). The calcium salt is the pharmaceutical form; the free acid is the synthetic and analytical reference form.

International Union of Pure and Applied Chemistry name: 4-[[[(2R)-2,4-dihydroxy-3,3-dimethyl-1-oxobutyl]amino]butanoic acid. The compound is the amide of D-pantoic acid (the open-chain form of D-pantolactone) and gamma-aminobutyric acid.

1.2 Structural class and chemistry

Hopantenic acid is a pantoyl amino acid conjugate belonging to the structural class of GABA analogs modified at the nitrogen by a pantoyl (2,4-dihydroxy-3,3-dimethylbutanoyl) acyl group. The compound is the direct homolog of pantothenic acid (vitamin B5), with the sole structural difference being the replacement of the

beta-alanine moiety of pantothenic acid (a three-carbon amino acid) with gamma-aminobutyric acid (a four-carbon amino acid), resulting in one additional methylene group in the chain [11].

Molecular formula: C₁₀H₁₉NO₅ (free acid); C₂₀H₃₆CaN₂O₁₀ (calcium salt, anhydrous).

Exact mass: 233.1263 g/mol (free acid, monoisotopic).

Molecular weight: 233.26 g/mol (free acid); 476.60 g/mol (calcium salt, anhydrous); 485.61 g/mol (calcium salt hemihydrate).

Physical properties: White to off-white crystalline powder. The free acid melts at approximately 62 to 64 degrees Celsius. The calcium salt is freely soluble in water and sparingly soluble in ethanol and most organic solvents. The compound is hygroscopic, particularly in the hemihydrate form. Optical rotation of the R-enantiomer (the pharmaceutically active form) is positive in aqueous solution, consistent with the D-pantoic acid configuration.

Stereochemistry: The pharmacologically active form is the R-enantiomer (D-hopantenic acid), corresponding to the natural D-configuration of pantoic acid and pantothenic acid. The S-enantiomer (L-hopantenic acid) has distinct pharmacological properties, including greater affinity for GABA-A receptors and dopamine D2 receptors. The racemic mixture (D,L-hopantenic acid) is formulated as Pantogam Active and displays a bimodal pharmacological profile combining the nootropic activity of the D-form with the anxiolytic activity of the L-form [12]. Investigators acquiring research-grade hopantenic acid should confirm enantiomeric configuration by chiral high-performance liquid chromatography or by polarimetry against a reference standard, as the pharmacological profiles of the two enantiomers differ substantially.

1.3 Synthesis

The standard synthesis of hopantenic acid proceeds through the condensation of D-pantolactone (the cyclic ester of D-pantoic acid, commercially available in high enantiomeric purity) with gamma-aminobutyric acid or its sodium salt [13]. The reaction involves nucleophilic ring opening of the lactone by the primary amine of GABA, forming the amide bond and producing hopantenic acid directly. The reaction is typically conducted by heating the reactants at elevated temperatures (approximately 130 to 140 degrees Celsius) in the absence of solvent or in a minimal

volume of water, for 12 to 18 hours. Acidification of the reaction mixture followed by lyophilization and purification by ion-exchange chromatography and flash chromatography yields hopantenic acid in approximately 70 to 78 percent yield. The calcium salt is prepared by neutralization of the free acid with calcium hydroxide or calcium carbonate in aqueous solution, followed by lyophilization or spray drying. Industrial syntheses (described in Soviet and Russian patents from the 1970s onward) optimize the condensation for yield, enantiomeric integrity, and removal of unreacted starting materials and lactone hydrolysis byproducts. The racemic form (D,L-hopantenic acid) is prepared by the same condensation using racemic pantolactone as the starting material.

2. Abstract

Hopantenic acid (homopantothenic acid, N-pantoyl-GABA) is a synthetic pantothenic acid homolog in which the beta-alanine component is extended by one methylene unit to gamma-aminobutyric acid, producing a molecule that retains structural recognition by pantothenic acid-metabolizing enzymes while simultaneously providing GABAergic pharmacological activity and the capacity to penetrate the blood-brain barrier [11]. The compound was first synthesized in Japan in the 1950s, entered clinical use as the calcium salt in Japan (1978) and the Soviet Union (1977), and is registered in the Russian Federation for a broad spectrum of neurological, psychiatric, and developmental indications in children and adults. The compound is not approved or registered in the United States, the European Union, or other Western regulatory jurisdictions.

The molecular pharmacology encompasses three principal domains. First, hopantenic acid acts as a weak GABA-B receptor agonist and, at higher concentrations, interacts with GABA-A receptors, producing mild anxiolytic, anticonvulsant, and sedative effects that are substantially weaker than those of direct GABAergic agents such as phenibut or benzodiazepines [14]. Second, the compound enhances cholinergic neurotransmission by increasing high-affinity choline transport into cortical and hippocampal synaptosomes and by stimulating choline acetyltransferase activity, as demonstrated in the Nakahiro et al. (1988) study in rat brain, providing a mechanistic basis for the nootropic and antidementia indications [1, 2]. Third, hopantenic acid is a competitive antagonist of pantothenic acid in the coenzyme A biosynthesis pathway; the compound is phosphorylated by pantothenate kinase to form phospho-hopantenic acid, which potently inhibits phosphopantothenoylcysteine synthetase (PPCS) and depletes cellular CoA levels [3]. This third mechanism is a double-edged property: at therapeutic doses and durations, the CoA pathway modulation may contribute to the compound's neuroprotective and metabolic-regulatory effects, but at high doses or with prolonged administration (particularly in vulnerable populations such as the elderly and young children), the pantothenic acid antagonism can produce a Reye-like syndrome of acute encephalopathy with hepatic steatosis, hyperammonemia, and hypoglycemia that was reported in multiple case series in Japan during the 1980s [4, 5, 6].

The principal clinical evidence base for hopantenic acid derives from Russian-language studies. The most methodologically robust trial is a multicenter, double-blind, placebo-controlled study in 100 children aged 6 to 12 years with attention deficit hyperactivity disorder, in which Pantogam at 30 mg/kg/day for four months produced statistically significant improvement on ADHD-DSM-IV rating scales and sustained attention measures compared to placebo, with a safety profile indistinguishable from placebo [8]. Additional clinical evidence supports the racemic formulation (Pantogam Active, D,L-hopantenic acid) for cognitive and anxiety disorders in patients with arterial hypertension and chronic cerebral ischemia, with rapid onset of cognitive and anxiolytic benefit within the first week of treatment at daily doses of 600 to 1200 mg for 28 days [9, 10]. The broader indication spectrum in Russian clinical practice includes cognitive impairment of cerebrovascular and neurodegenerative origin, perinatal encephalopathy, mental retardation, cerebral palsy, epilepsy (adjunctive), neurogenic bladder disorders (including enuresis), stuttering, and tic disorders [15].

Pharmacokinetics are characterized by rapid oral absorption (time to peak concentration approximately 1.5 hours), moderate bioavailability (approximately 64 percent in preclinical models), an elimination half-life of approximately 6.7 hours, and predominantly renal excretion of unchanged drug [7]. Hepatic metabolism is minimal, and no cytochrome P450 polymorphic phenotype analogous to the CYP2D6 dependence of tropisetron has been characterized.

This monograph documents the chemistry, synthesis, and stereochemistry; the multifaceted mechanism of action; the pharmacokinetic profile; the clinical evidence base; the Reye-like encephalopathy safety signal and its mechanistic basis; sourcing and quality verification; reconstitution and handling; stack interactions and combinations; adverse events; and a structured comparative assessment of five alternative nootropic and GABAergic compounds (piracetam, phenibut, GABA, pantothenic acid, and pramiracetam) against hopantenic acid on five standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 Origin

Hopantenic acid was first synthesized in Japan in the early 1950s as part of pantothenic acid analog research programs that explored structural variants of vitamin B5 for potential biological activity. The specific replacement of beta-alanine with gamma-aminobutyric acid was motivated by the hypothesis that a pantoyl-GABA conjugate would retain the vitamin-related metabolic activity of pantothenic acid while adding central nervous system pharmacological effects through the GABA moiety and improved blood-brain barrier penetration compared to free GABA [11]. Early Japanese pharmacological characterization in the 1960s demonstrated that the compound produced mild sedation, anticonvulsant activity, and enhancement of learning in animal models, leading to its classification as a nootropic agent.

3.2 Japanese development and registration

Calcium hopantenate was developed for clinical use in Japan during the 1970s and was registered in 1978 for the treatment of mental retardation and associated behavioral abnormalities. The compound was used in Japanese clinical practice primarily for pediatric neurological indications and for dementia in elderly patients. Clinical use expanded through the early 1980s with growing interest in the antidementia properties characterized by Nakahiro et al. (1988) and by earlier Japanese investigators who demonstrated enhancement of cholinergic markers in animal models [1, 2].

3.3 The Reye-like syndrome signal and withdrawal in Japan

Beginning in the mid-1980s, Japanese clinicians reported cases of acute encephalopathy with hepatic steatosis resembling Reye syndrome in patients receiving chronic calcium hopantenate therapy [4, 5]. Noda et al. (1988) described three senile patients who developed fatal acute encephalopathy with hyperammonemia, hypoglycemia, lactic acidemia, and microvesicular hepatic steatosis during calcium hopantenate treatment [5]. Noda et al. (1987) reported a 3-year-old girl with

similar findings [4]. Additional case reports described metabolic acidosis and hypoglycemia during therapy, and multiple cases of fatal encephalopathy were collected in Japanese adverse event reporting systems [6]. The mechanistic basis was identified as competitive antagonism of pantothenic acid in the CoA biosynthesis pathway, confirmed by Noda et al. (1991) in a dog model in which calcium hopantenate at escalating doses produced anorexia, vomiting, diarrhea, and ultimately coma with hepatic steatosis and mitochondrial abnormalities, all preventable by concurrent pantothenic acid administration [16]. The Reye-like syndrome signal led to substantial restriction of calcium hopantenate prescribing in Japan, and the compound was effectively withdrawn from widespread Japanese clinical use by the early 1990s.

3.4 Soviet and Russian development

Independent of the Japanese program, Soviet pharmacologists investigated hopantenic acid beginning in the 1960s, and the calcium salt was registered for clinical use in the Soviet Union in 1977. The Soviet development emphasized the nootropic, neuroprotective, and anticonvulsant properties of the compound and assigned it to the broader class of GABA-ergic nootropics alongside phenibut (beta-phenyl-GABA) and picamilon (nicotinoyl-GABA). The compound was developed under the brand name Pantogam by what is now PIQ-Pharma and was registered for an exceptionally broad range of neurological and psychiatric indications in children and adults [15]. The Russian clinical literature on hopantenic acid grew substantially through the 1990s and 2000s, with studies in cognitive impairment, ADHD, epilepsy, cerebral palsy, and neurogenic bladder disorders. In 2008, PIQ-Pharma introduced Pantogam Active, the racemic D,L-hopantenic acid formulation, with the stated pharmacological rationale that the L-enantiomer adds anxiolytic and enhanced neuroprotective activity through preferential GABA-A and dopamine D2 receptor interactions [12].

3.5 Current regulatory status

Hopantenic acid (as the calcium salt, Pantogam) is currently registered and marketed in the Russian Federation. The racemic formulation (Pantogam Active) is also registered in Russia. The compound is not approved by the United States Food and Drug Administration, the European Medicines Agency, or regulatory authorities in any Western jurisdiction. It is not listed in the United States Pharmacopeia, the

European Pharmacopoeia, or the British Pharmacopoeia. It is available from international research chemical suppliers as a reference compound and as a pharmaceutical-grade import from Russian manufacturers.

4. Mechanism of Action

Hopantenic acid is a multi-target compound whose pharmacological activity derives from three principal molecular mechanisms: GABAergic receptor modulation, cholinergic facilitation, and pantothenic acid pathway antagonism. These mechanisms operate at different concentration ranges and with different kinetics, producing a composite pharmacological profile that spans mild sedation, anxiolysis, anti-convulsant activity, cognitive enhancement, and metabolic modulation.

4.1 GABAergic receptor activity

The GABA moiety of hopantenic acid provides structural recognition at GABA receptors, although with substantially reduced potency compared to free GABA. In radioreceptor assays using [3H]-GABA as the radioligand, calcium hopantenate inhibited GABA receptor binding in a dose-dependent manner with a cross-reactive potency of approximately 0.2 percent relative to GABA itself [14]. The principal receptor subtype mediating the pharmacological effects at therapeutic concentrations is the GABA-B receptor, a G-protein coupled receptor that mediates slow inhibitory postsynaptic potentials and presynaptic inhibition of neurotransmitter release. Agonism at GABA-B produces the mild sedative, muscle-relaxant, and anti-convulsant effects observed in animal models and in clinical use.

At higher concentrations, the compound also interacts with GABA-A receptors (the ligand-gated chloride channel responsible for fast inhibitory neurotransmission). This interaction is more pronounced for the L-enantiomer than for the pharmacologically principal D-enantiomer, which is the basis for the enhanced anxiolytic profile of the racemic D,L-hopantenic acid formulation (Pantogam Active) [12]. The L-enantiomer additionally displays affinity for dopamine D2 receptors, a property that may contribute to the mild activating and mood-stabilizing effects reported in clinical use of the racemic form.

The GABAergic potency of hopantenic acid is substantially lower than that of phenibut (beta-phenyl-GABA), which has a K_i at GABA-B receptors of approximately 17 micromolar compared to the very weak binding of hopantenic acid. The clinical

consequence is that hopantenic acid produces milder sedation and less dependence liability than phenibut, positioning it as the mildest of the Soviet-developed GABAergic nootropics [14, 17].

4.2 Cholinergic facilitation

The second principal mechanism, and the basis for the nootropic and antidementia indications, is enhancement of cholinergic neurotransmission. Nakahiro et al. (1988) demonstrated that intraperitoneal administration of pantoyl-GABA (500 mg/kg, four doses at 30-minute intervals) to rats increased high-affinity choline transport into synaptosomes prepared from the cerebral cortex and hippocampus, but not from the striatum [1]. Choline concentration was increased in cortex and hippocampus, consistent with facilitated uptake. A related study demonstrated that pantoyl-GABA increased choline acetyltransferase activity in mouse brain, the rate-limiting enzyme in acetylcholine synthesis [2]. These findings indicate that hopantenic acid enhances the cholinergic synthetic capacity of cortical and hippocampal neurons, the brain regions most relevant to learning, memory, and cognitive processing.

The mechanism by which hopantenic acid enhances choline transport and acetyltransferase activity is not fully elucidated but is plausibly related to the pantothenate moiety of the molecule. Pantothenic acid is the precursor of coenzyme A, which in its acetyl-CoA form provides the acetyl group for acetylcholine synthesis by choline acetyltransferase. Hopantenic acid, through partial recognition by pantoyl-CoA metabolic enzymes, may facilitate the metabolic environment for acetylcholine synthesis while simultaneously providing mild GABAergic modulation. This dual mechanism (GABAergic plus cholinergic) is the molecular basis for the compound's classification as a nootropic with combined inhibitory and procognitive properties [11].

4.3 Pantothenic acid pathway antagonism and CoA modulation

The third mechanism is the interaction of hopantenic acid with the coenzyme A biosynthesis pathway. Hopantenic acid is a structural analog of pantothenic acid and is recognized by pantothenate kinase, the first enzyme in the five-step CoA biosynthesis pathway. Pantothenate kinase phosphorylates hopantenic acid to produce phospho-hopantenic acid, which then potently inhibits phosphopan-

tothenoylcysteine synthetase (PPCS), the second enzyme in the pathway [3]. The inhibition is competitive with respect to the natural substrate phosphopantothenate and produces a dose-dependent reduction in cellular CoA levels.

Zhang et al. (2007), using calcium hopantenate as a chemical tool to produce CoA depletion in mice, demonstrated that the compound inhibited mouse pantothenate kinase isoforms with IC₅₀ values between 50 and 150 micromolar and that chronic administration produced hepatic CoA depletion with compensatory upregulation of thioesterases (which liberate free CoA from acyl-CoA) and pyruvate dehydrogenase kinase 1 (which prevents conversion of free CoA to acetyl-CoA) [3]. These findings confirm that hopantenic acid is a functional pantothenic acid antagonist at the CoA biosynthesis level and that chronic high-dose administration can produce metabolically significant CoA depletion.

The CoA depletion mechanism is the molecular basis for the Reye-like encephalopathy syndrome observed in Japanese clinical practice and reproduced in the dog model [16]. CoA depletion impairs mitochondrial beta-oxidation of fatty acids (which requires CoA as the acyl carrier), the citric acid cycle (which requires acetyl-CoA as substrate), and the urea cycle (which requires N-acetylglutamate, synthesized from acetyl-CoA, for activation of carbamoyl phosphate synthetase I). The resulting metabolic cascade produces hepatic steatosis (from impaired fatty acid oxidation), hypoglycemia (from impaired gluconeogenesis), lactic acidemia (from impaired pyruvate oxidation), and hyperammonemia (from impaired urea cycle function), the complete biochemical picture of Reye syndrome [4, 5, 6].

At therapeutic doses and durations in adults and children with adequate nutritional status, the CoA depletion is modest and is balanced by compensatory metabolic adjustments. The encephalopathy risk is elevated in nutritionally compromised populations (the elderly, young children with restricted diets, patients with pre-existing hepatic disease) and with chronic high-dose administration. The preventability of the encephalopathy by concurrent pantothenic acid supplementation confirms that the mechanism is competitive antagonism at the pantothenate kinase step, not an irreversible enzymatic inhibition [16].

4.4 Composite pharmacology

The composite pharmacology of hopantenic acid at registered oral doses (250 to 1000 mg in adults, 250 to 500 mg in children) produces plasma concentrations sufficient for weak GABA-B receptor activation and for cholinergic facilitation, while

maintaining CoA levels within homeostatic limits. The nootropic effect is predominantly attributable to the cholinergic facilitation; the anxiolytic and anticonvulsant effects are attributable to the GABAergic activity; and the neuroprotective effects reported in animal models of cerebral ischemia are plausibly attributable to a combination of GABAergic neuronal stabilization and metabolic modulation through the pantothenate pathway [11, 14].

The racemic D,L-hopantenic acid formulation (Pantogam Active) provides a modified composite pharmacology in which the L-enantiomer contributes additional GABA-A receptor activity and dopamine D2 receptor interaction, producing a more pronounced anxiolytic and anticonvulsant profile than the D-enantiomer alone [12].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Hopantenic acid (as the calcium salt) is well absorbed from the gastrointestinal tract after oral administration. Time to peak plasma concentration is approximately 1.5 to 1.6 hours in preclinical models [7]. The absorption is rapid and is not substantially affected by food in the limited available characterization. Absolute oral bioavailability was determined to be approximately 64 percent in rat studies; human bioavailability data from controlled pharmacokinetic studies are limited in the English-language literature but are reported in Russian prescribing information to be consistent with the preclinical estimates.

5.2 Distribution

Distribution data in the English-language pharmacological literature are limited. The compound crosses the blood-brain barrier, a property that is the fundamental basis for its central nervous system pharmacology and that distinguishes it from free GABA (which does not cross the blood-brain barrier at pharmacologically relevant rates). The pantoyl moiety of the molecule is the structural feature that facilitates transport, likely through recognition by carrier-mediated transport systems for pantothenic acid and related compounds at the blood-brain barrier. Plasma protein binding has not been characterized in published English-language studies. The compound distributes to brain tissue at concentrations sufficient for the observed pharmacological effects, as demonstrated by the behavioral and neurochemical studies in rodents [1, 2].

5.3 Metabolism

Hopantenic acid undergoes minimal hepatic metabolism. The compound is not a substrate of the cytochrome P450 enzyme system in any characterized interaction study, and no CYP-mediated polymorphic metabolism analogous to the CYP2D6 dependence of tropisetron has been identified. The compound is excreted predomi-

nantly unchanged, indicating that the parent molecule is the active species and that metabolic activation (other than the phosphorylation by pantothenate kinase that produces the CoA pathway inhibitor) is not required for pharmacological activity [7].

5.4 Elimination

The elimination half-life is approximately 6.7 hours, and the compound is not detectable in plasma at 48 hours after a single oral dose [7]. Elimination is predominantly renal, with the unchanged compound excreted in urine. Biliary excretion accounts for a minor fraction. The renal elimination pathway suggests that dose adjustment may be appropriate in patients with significant renal impairment, although formal renal-impairment pharmacokinetic studies have not been published in the English-language literature.

5.5 Routes of administration

The principal route of administration is oral. The calcium salt is supplied as tablets (250 mg and 500 mg) and as an oral syrup (100 mg/mL) in the Russian pharmaceutical market. Pantogam Active (D,L-hopantenic acid) is supplied as 300 mg capsules. Parenteral formulations are not commercially available. The oral route is the only registered route of administration.

Typical dosing in Russian clinical practice for adults is 250 mg to 1000 mg per dose, taken two to three times daily, for total daily doses of 1500 to 3000 mg, with treatment courses of one to four months and in some cases up to six months [15]. Pediatric dosing is 250 to 500 mg per dose, with daily doses of 750 to 3000 mg depending on the indication and the child's body weight. The ADHD trial employed a dose of 30 mg/kg/day divided into two administrations [8].

5.6 Special populations

Pediatric pharmacokinetics have not been formally characterized in published English-language pharmacokinetic studies but are addressed in the Russian prescribing information. The compound is approved for pediatric use in the Russian Federation from age 3 years (syrup formulation) and from school age (tablet formulation). Geriatric pharmacokinetics are also not formally characterized; the Reye-like encephalopathy signal in elderly Japanese patients suggests that age-related re-

ductions in hepatic CoA reserves and nutritional pantothenic acid intake may increase vulnerability to the CoA depletion mechanism. Pregnancy and lactation data are limited; the Russian prescribing information lists pregnancy as a relative contraindication for the first trimester and recommends caution during lactation.

6. Clinical Evidence Base

6.1 Attention deficit hyperactivity disorder

The most methodologically robust clinical trial of hopantenic acid is a prospective, multicenter, double-blind, placebo-controlled, parallel-group study conducted in the Russian Federation assessing the efficacy and safety of Pantogam (calcium hopantenate) compared with placebo in 100 children aged 6 to 12 years with attention deficit hyperactivity disorder [8]. Pantogam was administered at 30 mg/kg/day, divided into two doses, for four months. Eighty-nine patients completed the study in compliance with the protocol (45 Pantogam, 44 placebo). Treatment response, defined as a decrease in the total ADHD-DSM-IV score by 25 percent or greater, was 68.9 percent in the Pantogam group and 61.4 percent in the placebo group at the end of the fourth month, a modest but consistent numerical advantage that reached statistical significance on the primary endpoint analysis. Pantogam significantly improved measures of sustained attention (accuracy and speed) on the Toulouse-Pieron test and produced a significant decrease in disease severity on the Clinical Global Impression-Severity scale compared to placebo. The safety profile was indistinguishable from placebo at the studied dose and duration.

A second study assessed hopantenic acid for hyperkinetic behavior disorder (hyperkinetic conduct disorder and ADHD combined type) and reported that combination of hopantenic acid with behavioral therapy improved outcomes compared to behavioral therapy alone, although this study was open-label and is subject to the corresponding methodological limitations [18].

6.2 Cognitive impairment in cerebrovascular disease

The racemic formulation (Pantogam Active, D,L-hopantenic acid) has been evaluated in open-label and controlled studies for cognitive and anxiety disorders in patients with arterial hypertension and chronic cerebral ischemia [9, 10]. In a study of 80 inpatients with hypertension and comorbid cognitive and anxiety disorders, the main group (n=50) received Pantogam Active at 600 to 1200 mg daily for 28 days, with a control group (n=30) receiving standard antihypertensive therapy alone. Significant reduction in both cognitive and anxiety disorder scores was observed in

the Pantogam Active group compared to controls, with a rapid onset of effect within the first week. A separate study in patients with chronic cerebral ischemia similarly reported significant reduction of anxiety, depression, and cognitive impairment during concomitant therapy with Pantogam Active [10].

These studies provide evidence for the bimodal nootropic-anxiolytic profile of the racemic formulation but are limited by open-label design, moderate sample sizes, and the absence of replication in non-Russian clinical settings.

6.3 Perinatal encephalopathy and developmental disorders

Hopantenic acid is prescribed in Russian clinical practice for perinatal encephalopathy, mental retardation of varying severity, and developmental delay (mental, speech, motor, or combinations thereof) in children. The evidence base for these indications is principally composed of Russian-language observational studies and case series rather than randomized controlled trials. The prescribing rationale is the cholinergic facilitation mechanism and the mild activating nootropic effect, which are expected to support neurodevelopmental maturation in children with delayed milestones.

6.4 Epilepsy

Hopantenic acid is used as adjunctive therapy in epilepsy in Russian clinical practice, particularly to counteract the cognitive side effects of antiepileptic drugs. The anticonvulsant activity of the compound (mediated through GABAergic mechanisms) and the nootropic activity (mediated through cholinergic facilitation) provide a theoretical rationale for this application. The clinical evidence consists of observational reports; no randomized controlled trial of hopantenic acid as epilepsy adjunctive therapy has been identified in the English-language literature.

6.5 Neurogenic bladder and enuresis

Hopantenic acid is registered in the Russian Federation for neurogenic bladder disorders including pollakiuria, urgency, imperative urinary incontinence, and enuresis in children [15]. The pharmacological rationale for the urological indication is the GABAergic modulation of bladder control circuitry and the mild sedative effect. Clinical evidence is from Russian observational studies.

6.6 Tic disorders and stuttering

Hopantenic acid is prescribed for tic disorders and stuttering (predominantly the clonic form) in children in Russian clinical practice. The GABAergic anxiolytic and mild sedative properties provide the pharmacological rationale. Clinical evidence is from Russian observational studies and case series.

6.7 Postoperative cognitive dysfunction in children

A published study assessed hopantenic acid for correction of cognitive disorders in the postoperative period in children, reporting improvement in cognitive measures following surgical procedures under general anesthesia [19]. The neuroprotective and nootropic mechanisms are the pharmacological rationale for this application.

7. Reported Research Dose Ranges

7.1 Approved doses (Russian Federation)

Adult indications: 250 mg to 1000 mg per dose, two to three times daily. Total daily dose ranges from 1500 to 3000 mg depending on indication and severity. Treatment courses of one to four months are standard, with extension to six months in some indications [15].

Pediatric indications: 250 to 500 mg per dose. Total daily doses of 750 to 3000 mg depending on the child's age, body weight, and indication. The ADHD trial dosing was 30 mg/kg/day divided into two doses [8].

Pantogam Active (D,L-hopantenic acid): 300 mg capsules, with daily doses of 600 to 1800 mg (two to six capsules) divided into two to three administrations. The arterial hypertension cognitive study employed 600 to 1200 mg daily for 28 days [9].

7.2 Investigational and research doses

Preclinical studies have employed doses ranging from 100 to 500 mg/kg intraperitoneally in rodents. The Nakahiro et al. (1988) study used 500 mg/kg intraperitoneally in rats (four doses at 30-minute intervals) to characterize choline transport enhancement [1]. The Zhang et al. (2007) CoA depletion study used chronic administration in mice at doses sufficient to produce hepatic CoA depletion [3].

Investigators acquiring research-grade hopantenic acid should note that the therapeutic doses in Russian clinical practice (1500 to 3000 mg daily in adults) are substantially higher than the typical doses of many Western nootropic compounds, reflecting the relatively low potency of the compound at its target receptors.

8. Sourcing and Quality Verification

Pharmaceutical-grade hopantenic acid (calcium salt) is available as Pantogam tablets (250 mg, 500 mg) and syrup (100 mg/mL) and as Pantogam Active capsules (300 mg, D,L-hopantenic acid) from Russian pharmaceutical distributors and from international pharmacy services that export Russian medications. Pharmaceutical-grade material meets Russian Pharmacopoeia standards.

Research-grade hopantenic acid (free acid and calcium salt) is available from multiple research chemical suppliers (BenchChem, Sigma-Aldrich, Santa Cruz Biotechnology, Cayman Chemical, Tokyo Chemical Industry, others) at greater than 95 to 98 percent purity by HPLC. Supply is in milligram to gram quantities. Pricing is moderate, typically in the range of \$30 to \$150 per gram depending on supplier and quantity.

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 (234.13 for the protonated free acid $[M+H]^+$, or 233.13 for the molecular ion)
- Chiral HPLC or polarimetry to confirm the D-configuration (R-enantiomer) when the enantiopure form is specified; the racemic form should show absence of optical rotation
- Karl Fischer or loss-on-drying analysis for residual water content (the hemihydrate is the common solid form of the calcium salt)
- Residual solvent analysis for common synthesis solvents

Third-party analytical confirmation is appropriate for investigations where dose-response precision is important, given the relatively limited analytical standardization of this compound in Western research contexts compared to established Western pharmaceuticals.

9. Reconstitution and Handling

Hopantenic acid (calcium salt) is freely soluble in water at room temperature. For research applications, the compound is supplied as a crystalline or lyophilized powder. Stock solutions are typically prepared at 10 to 100 mg/mL in water, phosphate-buffered saline, or dimethyl sulfoxide (for in vitro applications where higher concentrations are required).

Storage of the solid form should be at room temperature (15 to 25 degrees Celsius) in a dry environment, protected from moisture due to the hygroscopic nature of the calcium salt (particularly the hemihydrate form). The compound is stable under these conditions for at least two years as the solid.

Aqueous stock solutions should be stored at 2 to 8 degrees Celsius and used within 14 days of preparation. The compound is stable in neutral to mildly acidic aqueous solution; strongly alkaline conditions may promote hydrolysis of the amide bond. Aliquoting of stock solutions for single-use is recommended to avoid repeated freeze-thaw cycles, although the compound is generally tolerant of freeze-thaw cycling (at least three to five cycles without measurable potency loss) due to its simple, stable amide structure.

For cell culture and in vitro applications, the aqueous stock solution should be sterilized by filtration through a 0.22-micron syringe filter. The compound does not adsorb significantly to standard laboratory plastics or to glass.

10. Stack Interactions and Combinations

Hopantenic acid interacts with several compound classes through its multifaceted mechanism and its position in the pantothenic acid metabolic pathway. Investigators conducting research with hopantenic acid in combination protocols should consider the following interactions.

Pantothenic acid (vitamin B5): Concurrent pantothenic acid administration is protective against the CoA depletion toxicity of hopantenic acid and is the basis of the recommended safety measure of ensuring adequate pantothenic acid nutritional status during chronic hopantenic acid administration [16]. Pharmacological doses of pantothenic acid (100 to 500 mg daily) have been used experimentally as a concurrent supplement to mitigate CoA depletion risk during high-dose or long-duration hopantenic acid protocols.

Other GABAergic agents (phenibut, baclofen, benzodiazepines, gabapentin, pregabalin): Concurrent GABAergic agents produce additive sedation, anxiolysis, and muscle relaxation. The combination of hopantenic acid with phenibut is used in Russian clinical practice for anxiety-predominant presentations, but the additive GABA-B agonism increases sedation and dependence risk (primarily from the phenibut component). The combination with benzodiazepines increases central nervous system depression. Baclofen (a potent GABA-B agonist) produces pharmacologically redundant GABA-B activation and should be combined with caution.

Cholinergic agents (donepezil, rivastigmine, galantamine): The cholinergic facilitation by hopantenic acid (increased choline transport and acetyltransferase activity) may produce additive cholinergic effects when combined with acetylcholinesterase inhibitors. This combination is pharmacologically rational for cognitive enhancement research but may produce additive parasympathomimetic adverse events (nausea, diarrhea, salivation, bradycardia).

Anticholinergic agents: Anticholinergic drugs (trihexyphenidyl, benztropine, diphenhydramine, older tricyclic antidepressants) may antagonize the cholinergic facilitation that is the principal nootropic mechanism of hopantenic acid, potentially reducing cognitive benefit.

Antiepileptic drugs: Hopantenic acid is used adjunctively with antiepileptic drugs in Russian clinical practice to counteract cognitive side effects. No significant pharmacokinetic interactions have been reported, consistent with the absence of CYP450-mediated metabolism of hopantenic acid. The GABAergic activity of hopantenic acid may provide mild additive anticonvulsant effect.

Other nootropics (piracetam, pramiracetam, aniracetam): Combination with racetam-class nootropics is common in Russian and Eastern European nootropic practice. The mechanisms are complementary (GABAergic and cholinergic for hopantenic acid; glutamatergic and AMPA-mediated for racetams), and no adverse interactions have been reported.

Alcohol: Concurrent ethanol consumption with hopantenic acid produces additive central nervous system depression through combined GABAergic mechanisms. The combination should be avoided during active treatment.

11. Adverse Events and Safety

11.1 Common adverse events

At registered doses and standard treatment durations, hopantenic acid is well tolerated. The safety profile from the Russian clinical literature and from the ADHD placebo-controlled trial reports the following common adverse events [8, 15]:

- Drowsiness and mild sedation (particularly in the first days of treatment; dose-dependent)
- Allergic skin reactions (urticaria, rash; rare, less than 1 percent)
- Rhinitis and conjunctivitis (allergic-type reactions; rare)
- Headache (infrequent)
- Gastrointestinal discomfort (nausea, mild abdominal pain; infrequent)

The ADHD trial reported a safety profile indistinguishable from placebo at 30 mg/kg/day for four months, with no clinically significant laboratory abnormalities [8].

11.2 Rare and serious adverse events: the Reye-like encephalopathy

The most serious adverse effect associated with hopantenic acid is the Reye-like syndrome of acute encephalopathy with hepatic steatosis reported in Japanese clinical practice during the 1980s [4, 5, 6]. The syndrome is characterized by:

- Acute onset of altered consciousness progressing to coma
- Hyperammonemia
- Hypoglycemia
- Metabolic (lactic) acidosis
- Elevated serum transaminases
- Microvesicular hepatic steatosis on biopsy or autopsy
- Mitochondrial structural abnormalities in hepatocytes

The cases occurred predominantly in elderly patients on chronic therapy and in young children, populations likely to have reduced hepatic CoA reserves and marginal nutritional pantothenic acid status. The Noda et al. (1991) dog model reproduced the complete syndrome at escalating doses over 8 weeks and demonstrated prevention by concurrent pantothenic acid administration [16]. The estimated incidence of the encephalopathy in Japanese clinical practice was not formally quantified but was sufficient to lead to effective withdrawal of the compound from widespread Japanese use.

The encephalopathy has not been reported at comparable frequency in the Russian clinical literature, a discrepancy that may reflect differences in prescribing practices (lower doses, shorter durations, different patient populations), differences in reporting systems, or concurrent nutritional supplementation. Russian prescribing information does not prominently feature the Reye-like syndrome risk but does note that adequate nutritional status should be maintained during treatment.

11.3 Contraindications

Russian prescribing information lists the following contraindications: first trimester of pregnancy, severe renal impairment (creatinine clearance less than 30 mL/min), and known hypersensitivity to the compound or its components [15]. Relative contraindications include hepatic insufficiency and conditions associated with marginal pantothenic acid nutritional status.

11.4 Dependence and withdrawal

Hopantenic acid does not produce physical dependence or withdrawal symptoms at registered doses, distinguishing it from other GABAergic agents such as phenibut and benzodiazepines. This absence of dependence liability is attributed to the very low potency of the compound at GABA receptors compared to dedicated GABA agonists [14, 17].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative nootropic and GABAergic compounds against hopantenic acid, evaluated on five standards: novelty, effect size, promising potential (current clinical and research trajectory), side-effect profile, and overall validation. The five compounds were selected to span the structural and mechanistic landscape of GABAergic nootropics and related agents that share one or more of hopantenic acid's principal mechanisms.

12.1 Piracetam

Mechanism: Piracetam (2-oxo-1-pyrrolidineacetamide) is a cyclic derivative of GABA that is the prototype of the racetam class of nootropics. Despite its GABA-derived structure, piracetam does not bind GABA receptors at pharmacologically relevant concentrations. Its mechanism involves modulation of AMPA-type glutamate receptors (positive allosteric modulation), enhancement of membrane fluidity, modulation of neurotransmitter release (acetylcholine, glutamate), and improvement of cerebral blood flow through effects on erythrocyte deformability and platelet aggregation [20].

Development trajectory: Piracetam was synthesized by Corneliu Giurgea at UCB Pharmaceuticals in Belgium in 1964 and was the compound for which the term "nootropic" was coined. It has been registered in numerous European and Asian jurisdictions for cognitive impairment, vertigo, and adjunctive epilepsy therapy, though it has never been approved by the FDA. The compound has an extensive clinical literature spanning more than five decades.

Novelty: Low. Piracetam is the founding member of the nootropic class and the most extensively characterized compound in the category.

Effect size: Modest. Meta-analyses of piracetam in cognitive impairment in dementia have reported statistically significant but small-to-moderate effect sizes on global cognitive measures. A Cochrane review of piracetam in dementia concluded that piracetam produced a statistically significant positive effect on the Clinical

Global Impression of Change, but the clinical significance of the magnitude was uncertain [21]. Effect sizes in age-related cognitive decline and in healthy volunteers are smaller still.

Promising potential: Moderate. The compound remains available and is prescribed in many jurisdictions, but active new clinical development is minimal. Research interest is principally in combination protocols and in phenotypic screening for next-generation racetams.

Side-effect profile: Favorable. Piracetam is well tolerated at doses of 1200 to 4800 mg daily, with principal adverse events being mild gastrointestinal discomfort, insomnia, and agitation. No serious safety signal analogous to the hopantenic acid Reye-like encephalopathy has been identified.

Overall validation: Moderate to high. Piracetam has the most extensive clinical evidence base of any nootropic compound, with multiple randomized controlled trials and meta-analyses, though effect sizes have been consistently modest.

Comparison to hopantenic acid: Piracetam and hopantenic acid occupy overlapping clinical indications (cognitive impairment, age-related cognitive decline) but have fundamentally different mechanisms: piracetam acts through glutamatergic and membrane-related effects, while hopantenic acid acts through GABAergic and cholinergic mechanisms with CoA pathway modulation. Piracetam has a substantially stronger evidence base in Western clinical literature and a more favorable safety profile (absence of CoA depletion toxicity). Hopantenic acid has the advantage of a combined anxiolytic-nootropic profile that piracetam lacks. The two compounds are often combined in Russian clinical practice.

12.2 Phenibut (beta-phenyl-GABA)

Mechanism: Phenibut (4-amino-3-phenylbutyric acid) is a GABA analog with a phenyl substituent on the beta-carbon that confers blood-brain barrier penetration and approximately 100-fold greater potency at the GABA-B receptor compared to unsubstituted GABA. The compound acts as a GABA-B receptor agonist (K_i approximately 17 micromolar), a weak GABA-A receptor agonist at high concentrations, and a voltage-dependent calcium channel blocker. It also antagonizes beta-phenethylamine, a putative endogenous anxiogenic [17].

Development trajectory: Synthesized in the Soviet Union in the 1960s by Perekalin at the Herzen Pedagogical Institute in Leningrad, phenibut was registered in the USSR in 1975 and remains registered in the Russian Federation and several former Soviet states for anxiety, insomnia, and vestibular disorders. It is not approved in any Western jurisdiction but is widely available as a dietary supplement in the United States and other markets.

Novelty: Low. The mechanism is conventional GABAergic agonism, representing an earlier generation of Soviet GABA-analog pharmacology.

Effect size: Moderate for anxiolysis and moderate for sleep improvement. Clinical trials in the Soviet and Russian literature report significant anxiolytic and sleep-promoting effects. Cognitive enhancement effect sizes are small and inconsistent.

Promising potential: Low as a pharmaceutical development candidate; high as a commercially available supplement, though regulatory scrutiny in Western markets is increasing due to abuse potential.

Side-effect profile: Less favorable than hopantenic acid. Phenibut produces dose-dependent sedation, dizziness, and gastrointestinal effects at therapeutic doses. The principal safety concern is dependence and withdrawal: chronic use at supraphysiological doses produces physical dependence with a withdrawal syndrome that includes anxiety, insomnia, tremor, and in severe cases psychosis, resembling benzodiazepine or alcohol withdrawal. This dependence liability is the most important clinical distinction from hopantenic acid.

Overall validation: Low to moderate. The clinical evidence base is composed primarily of Soviet-era and Russian studies of variable methodological quality. Western clinical evidence is minimal.

Comparison to hopantenic acid: Phenibut is a more potent anxiolytic than hopantenic acid but lacks the nootropic (cholinergic facilitation) and metabolic (CoA pathway) mechanisms of hopantenic acid and has a substantially worse dependence and withdrawal profile. Hopantenic acid is the preferred agent for cognitive enhancement with mild anxiolysis; phenibut is the preferred agent for acute anxiety when dependence risk is managed. The two compounds are sometimes combined in Russian clinical practice but the combination increases GABAergic sedation and phenibut dependence risk.

12.3 GABA (gamma-aminobutyric acid)

Mechanism: GABA is the principal inhibitory neurotransmitter in the mammalian central nervous system, acting at GABA-A (ligand-gated chloride channels) and GABA-B (G-protein-coupled) receptors throughout the brain and spinal cord. As an exogenously administered compound, GABA does not cross the blood-brain barrier at pharmacologically relevant rates in healthy adults, severely limiting its utility as a centrally acting agent [22].

Development trajectory: GABA has been available as a dietary supplement and as a pharmaceutical-grade research compound for decades. It is marketed as a supplement for stress and sleep support, primarily in Japan and in the global dietary supplement market. It is not registered as a pharmaceutical drug for central nervous system indications in any major jurisdiction.

Novelty: None. GABA is the endogenous neurotransmitter itself.

Effect size: Minimal for central nervous system effects when administered orally, due to negligible blood-brain barrier penetration. Some evidence suggests peripheral effects (modulation of enteric nervous system, adrenal hormone modulation) that may produce mild relaxation through indirect mechanisms, but central nootropic or anxiolytic effects at oral supplement doses have not been convincingly demonstrated in controlled studies.

Promising potential: Low for central nervous system applications. The blood-brain barrier impermeability is a fundamental pharmacological limitation that cannot be overcome by dose escalation.

Side-effect profile: Excellent. Oral GABA supplementation is well tolerated at typical supplement doses (100 to 750 mg) with no significant adverse events reported. The absence of central nervous system penetration limits both efficacy and toxicity.

Overall validation: Low for central nervous system indications.

Comparison to hopantenic acid: GABA is the structural and pharmacological parent compound of hopantenic acid but is fundamentally limited by blood-brain barrier impermeability. The pantoyl conjugation that produces hopantenic acid is precisely the modification that overcomes this limitation and enables central ner-

vous system activity. Hopantenic acid is therefore the pharmacologically functional form of the GABA nootropic concept, with actual blood-brain barrier penetration and demonstrated central effects.

12.4 Pantothenic acid (vitamin B5)

Mechanism: Pantothenic acid is an essential water-soluble vitamin that serves as the precursor of coenzyme A (CoA) and acyl carrier protein (ACP), both of which are central to fatty acid metabolism, the citric acid cycle, and numerous biosynthetic pathways including acetylcholine synthesis [23]. Pantothenic acid does not have direct receptor-mediated pharmacological activity at GABA or other neurotransmitter receptors.

Development trajectory: Pantothenic acid is a long-established essential nutrient with defined adequate intake values (5 mg/day for adults) and is available in supplement and pharmaceutical-grade forms worldwide. Pharmacological doses (100 to 1000 mg daily) have been investigated for dyslipidemia (as the pantethine derivative), wound healing, and acne, with variable results.

Novelty: None for the parent vitamin; moderate for derivatives such as pantethine and for the concept of CoA pathway optimization.

Effect size: No direct nootropic effect has been demonstrated for pantothenic acid supplementation in individuals with adequate nutritional intake. In pantothenic acid deficiency (rare in developed populations), supplementation reverses the neurological symptoms (burning feet syndrome, fatigue, irritability), confirming the vitamin's role in central nervous system function through CoA-dependent pathways.

Promising potential: Low as a stand-alone nootropic. Moderate as a concurrent supplement to mitigate the CoA depletion risk of hopantenic acid therapy.

Side-effect profile: Excellent. Pantothenic acid is well tolerated at doses up to 1000 mg daily with no significant adverse events. Diarrhea is the principal adverse event at very high doses.

Overall validation: High as an essential nutrient; low as a stand-alone nootropic.

Comparison to hopantenic acid: Pantothenic acid is the structural parent of hopantenic acid (differing only in the replacement of beta-alanine with GABA) and is the metabolic competitor at the pantothenate kinase step of CoA biosynthesis. The two compounds have an antagonistic relationship in CoA metabolism, which is both the source of hopantenic acid's toxicity and the rationale for concurrent pantothenic acid supplementation as a safety measure. Pantothenic acid provides the CoA-dependent metabolic support for acetylcholine synthesis but lacks the direct GABAergic receptor activity that is central to hopantenic acid's anxiolytic and anti-convulsant pharmacology.

12.5 Pramiracetam

Mechanism: Pramiracetam (N-[2-(diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide) is a lipophilic racetam derivative with approximately 5- to 10-fold greater potency than piracetam in behavioral models of cognitive enhancement. The mechanism involves enhancement of high-affinity choline uptake in the hippocampus, a mechanism that is shared with hopantenic acid, plus modulation of acetylcholine release and AMPA receptor-mediated glutamatergic neurotransmission [24]. Pramiracetam does not bind GABA receptors.

Development trajectory: Developed by Parke-Davis (now Pfizer) in the 1970s, pramiracetam was investigated in Phase 2 trials for Alzheimer's disease and for cognitive impairment following traumatic brain injury, with positive signals in small studies. It is registered in some European countries (Italy, several Eastern European jurisdictions) for cognitive impairment. It has never been approved by the FDA.

Novelty: Low to moderate. The mechanism is a refinement of the piracetam concept with enhanced potency and lipophilicity.

Effect size: Moderate. Pramiracetam has demonstrated significant cognitive enhancement in healthy volunteers (Mauri et al. 1994) and in traumatic brain injury patients at doses of 1200 to 4800 mg daily, with effect sizes in the moderate range for memory and attention measures [24].

Promising potential: Low to moderate. Active pharmaceutical development has ceased, but the compound remains available as a research tool and as a registered medicine in limited jurisdictions.

Side-effect profile: Favorable. Principal adverse events are headache and gastrointestinal discomfort. No serious safety signal analogous to the hopantenic acid Reye-like encephalopathy has been identified.

Overall validation: Low to moderate. The clinical evidence base is small but positive, with higher-quality studies than most racetam derivatives.

Comparison to hopantenic acid: Pramiracetam and hopantenic acid share the mechanism of high-affinity choline uptake enhancement but differ in their secondary mechanisms: pramiracetam is glutamatergic, while hopantenic acid is GABAergic. Pramiracetam has a more favorable safety profile (absence of CoA depletion toxicity) and higher potency at the cholinergic mechanism. Hopantenic acid has the advantage of combined anxiolytic-nootropic activity that pramiracetam lacks and a broader registered indication spectrum (in Russia). The two compounds are mechanistically complementary and could be combined in research protocols to test the hypothesis that dual cholinergic facilitation (via different upstream mechanisms) produces synergistic cognitive enhancement.

12.6 Comparator summary

The five comparator compounds span the mechanistic landscape surrounding hopantenic acid. **Piracetam** is the reference nootropic with the largest evidence base but lacks anxiolytic and GABAergic activity. **Phenibut** is the most potent anxiolytic of the set but carries dependence risk absent from hopantenic acid. **GABA** is the parent neurotransmitter but is centrally inactive when administered orally. **Pantothenic acid** is the metabolic parent compound and the critical safety cofactor for mitigating hopantenic acid toxicity. **Pramiracetam** shares the cholinergic facilitation mechanism with greater potency and a better safety profile but without GABAergic activity.

Hopantenic acid occupies a unique position in this landscape as the only compound that combines GABAergic receptor activity, cholinergic facilitation, and pantothenic acid pathway modulation in a single molecule. This multifaceted mechanism is both its principal pharmacological distinction and the source of its most serious safety concern (CoA depletion). The compound's clinical evidence base is weaker than piracetam's by Western methodological standards but is substantial within the Russian pharmacological literature. The absence of dependence liability distinguishes it favorably from phenibut, and the ability to cross the blood-brain barrier distinguishes it fundamentally from free GABA.

The principal practical consideration for investigators is the Reye-like encephalopathy risk, which is specific to hopantenic acid among the comparators and which requires concurrent attention to pantothenic acid nutritional status, dose limitation, and treatment duration, particularly in vulnerable populations. With these precautions, hopantenic acid offers a mechanistically distinctive research tool for the investigation of combined GABAergic and cholinergic neuropharmacology.

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