

RESEARCH MONOGRAPH . COMPOUND PROFILE

Fasoracetam

A synthetic pyrrolidone nootropic developed at Nippon Shinyaku as a cognition enhancer for vascular dementia, distinguished from other racetams by GABA-B receptor upregulation, metabotropic glutamate receptor activation across all three mGluR groups, and facilitation of high-affinity choline uptake in the cerebral cortex and hippocampus.

DOCUMENT	KDC-MN-1431
ISSUED	2026-05-11
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Pyrrolidone-class racetam nootropic with GABA-B receptor upregulation, metabotropic glutamate receptor modulation, and cholinergic enhancement activity

ABSTRACT

Fasoracetam (NS-105, NFC-1, LAM-105) is a synthetic nootropic of the racetam family, defined structurally as (5R)-5-(piperidine-1-carbonyl)pyrrolidin-2-one and distinguished from the canonical racetam piracetam by the substitution of a piperidine amide at the 5-position of the 2-pyrrolidinone ring. The compound was synthesized at Nippon Shinyaku Co., Ltd. in the mid-1980s and advanced through Phase 3 clinical trials in Japan for vascular dementia, an indication in which it failed to demonstrate statistically significant efficacy on cognitive endpoints and was subsequently abandoned by the originator. The pharmacological profile comprises three principal mechanisms: upregulation of gamma-aminobutyric acid type B (GABA-B) receptors in the cerebral cortex following repeated administration; activation of metabotropic glutamate receptors (mGluRs) across all three receptor groups (Group I, Group II, and Group III); and facilitation of cholinergic neurotransmission through enhanced high-affinity choline uptake and increased acetylcholine release from cortical and hippocampal neurons. These mechanisms were characterized in a series of rat studies conducted at Nippon Shinyaku during the 1990s, with the GABA-B upregulation and learned helplessness reversal reported by Oguchi et al. (1998), the cholinergic facilitation and anti-amnestic activity reported by Maeda et al. (1997), and the involvement of both cholinergic and GABAergic systems in memory disruption reversal confirmed by Ito et al. (1999). Preclinical pharmacology demonstrates reversal of scopolamine-induced amnesia in passive avoidance and radial arm maze paradigms, reversal of baclofen-induced amnesia, reduction of immobility time in the forced swimming test, and

rescue of escape failure in the learned helplessness paradigm, with minimum effective doses as low as 0.1 mg/kg intraperitoneally for the active (5R) enantiomer. The compound was repurposed for attention deficit hyperactivity disorder (ADHD) following its acquisition by NeuroFix, Inc., which obtained the Nippon Shinyaku clinical data package and advanced the compound under the designation NFC-1. A five-week open-label, single-blind, placebo-controlled Phase 1/2 study in 30 adolescents with ADHD harboring mutations in mGluR network genes (Elia et al. 2018, Nature Communications) reported significant improvement on Clinical Global Impressions scales and parental Vanderbilt Assessment scores, with dose-proportional pharmacokinetics across the 50 to 800 mg dose range, a plasma elimination half-life of approximately 4 to 7 hours, rapid oral absorption with peak plasma concentrations at 1.3 to 1.9 hours, and oral bioavailability of 79 to 97 percent. The compound undergoes minimal hepatic metabolism and is excreted predominantly unchanged through the kidneys. There were no differences in adverse event incidence between placebo and active treatment weeks. Despite the ADHD pharmacogenomic signal, subsequent development has not produced a registration-enabling efficacy demonstration. NeuroFix was acquired by Medgenics (later Aevi Genomic Medicine, later Avalo Therapeutics), and development of fasoracetam for ADHD was deprioritized following disappointing efficacy results at scale. As of the most recent monograph revision, fasoracetam is under Phase 2 investigation by Nobias Therapeutics for 22q11.2 deletion syndrome (DiGeorge syndrome). The compound is not approved by any regulatory authority worldwide and is not marketed as a medicine. It is available as a research-grade preparation from multiple chemical suppliers. Investigators should obtain analytical confirmation of

identity, purity, and enantiomeric configuration on every lot, as the (5R) enantiomer is the active isomer and the racemic mixture has reduced potency.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Fasoracetam.

Development codes: NS-105 (Nippon Shinyaku Co., Ltd.; the canonical identifier in the originator pharmacology literature). NFC-1 (NeuroFix, Inc.; the identifier used in the ADHD clinical program and in the Elia et al. 2018 Nature Communications publication). LAM-105 (alternative designation appearing in some regulatory filings). AEVI-001 (Aevi Genomic Medicine designation).

Chemical Abstracts Service registry number: 110958-19-5.

International Union of Pure and Applied Chemistry name: (5R)-5-(piperidine-1-carbonyl)pyrrolidin-2-one. The compound is the piperidinamide of 5-oxo-D-proline (D-pyroglutamic acid), placing it within the racetam family defined by the shared 2-pyrrolidinone (gamma-lactam) pharmacophore.

Other chemical names: 5-oxo-D-prolinepiperidinamide; (R)-1-((5-oxo-2-pyrrolidinyl)carbonyl)piperidine; (5R)-5-(piperidin-1-ylcarbonyl)pyrrolidin-2-one.

PubChem CID: 198695.

DrugBank ID: DB16163.

UNII: 42O8UF5CJB.

1.2 Structural class and chemistry

Fasoracetam is a member of the racetam class of synthetic nootropics, all of which share a 2-pyrrolidinone (gamma-lactam) core. The racetam class includes piracetam (the progenitor), aniracetam, oxiracetam, pramiracetam, coluracetam, nefiracetam, and phenylpiracetam, among others. Fasoracetam is distinguished from the canonical racetam structure by replacement of the acetamide side chain at the 2-position (as in piracetam) with a piperidine-1-carbonyl substituent at the 5-position of the pyrrolidinone ring. This structural modification produces a conforma-

tionally constrained, lipophilic amide that alters the receptor interaction profile relative to simpler racetams and confers selectivity for GABA-B receptor modulation and mGluR activation that is not observed with piracetam or aniracetam [1, 2].

Molecular formula: C₁₀H₁₆N₂O₂.

Exact mass: 196.1212 g/mol (monoisotopic).

Molecular weight: 196.25 g/mol.

Physical properties: White to off-white crystalline powder. Soluble in water, methanol, and dimethyl sulfoxide; moderately soluble in ethanol. Melting point approximately 118 to 121 degrees Celsius.

Stereochemistry: Fasoracetam contains one stereocenter at carbon 5 of the pyrrolidinone ring and is supplied as the single (5R) enantiomer, corresponding to the D-configuration of the pyroglutamic acid precursor. The (5R) enantiomer is the pharmacologically active form. The (5S) enantiomer (derived from L-pyroglutamic acid) is substantially less active in preclinical cognitive models; minimum effective doses for the active isomer are as low as 0.1 mg/kg intraperitoneally compared to greater than 1 mg/kg for the (5S) form in rat passive avoidance paradigms [3]. Investigators acquiring research-grade fasoracetam should confirm enantiomeric purity by chiral high-performance liquid chromatography or by optical rotation measurement.

1.3 Synthesis

The synthesis of fasoracetam proceeds from D-pyroglutamic acid (5-oxo-D-proline), a commercially available chiral building block. The standard approach involves activation of the carboxylic acid moiety of D-pyroglutamic acid (or a suitably protected derivative) followed by amide bond formation with piperidine [3, 4]. Activation methods include carbodiimide-mediated coupling (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or 1,3-dicyclohexylcarbodiimide with hydroxybenzotriazole), mixed anhydride methods (isobutyl chloroformate), or acyl chloride formation. The coupling reaction proceeds in high yield (typically 75 to 90 percent) under mild conditions. The product is purified by recrystallization from ethanol, ethyl acetate, or isopropanol, or by silica gel chromatography for research-scale preparations. The enantiomeric purity of the product reflects the enantiomeric purity of the D-pyroglutamic acid starting material, which is typically greater than 99 percent enantiomeric excess when sourced from reputable chemi-

cal suppliers. Industrial synthesis optimizes the coupling step for scale and minimizes racemization at the alpha-carbon, which is negligible under standard amide-bond formation conditions owing to the cyclic constraint of the pyrrolidinone ring [4].

2. Abstract

Fasoracetam (NS-105, NFC-1) is a synthetic nootropic of the racetam class, structurally defined as the piperidinamide of 5-oxo-D-proline and pharmacologically characterized by a triple-mechanism profile comprising GABA-B receptor upregulation, metabotropic glutamate receptor modulation, and facilitation of cholinergic neurotransmission [1, 2, 5]. The compound was synthesized at Nippon Shinyaku Co., Ltd. in the mid-1980s, with the earliest patent priority dating to January 1986, and was advanced through Phase 3 clinical trials in Japan for the treatment of cognitive impairment associated with vascular dementia. The Phase 3 program, which enrolled several hundred patients across multiple Japanese centers and evaluated doses of 100 to 800 mg daily over treatment periods of 12 to 24 weeks, failed to demonstrate statistically significant improvement on cognitive endpoints (including the Alzheimer's Disease Assessment Scale cognitive subscale) relative to placebo. Nippon Shinyaku discontinued the vascular dementia program, reportedly after an investment exceeding 200 million United States dollars [6].

The compound was subsequently acquired by NeuroFix, Inc. (founded circa 2013), which obtained the complete Nippon Shinyaku preclinical and clinical data package and repurposed fasoracetam for attention deficit hyperactivity disorder (ADHD) under the designation NFC-1, with a pharmacogenomic stratification strategy targeting adolescents carrying mutations in genes encoding metabotropic glutamate receptor network components [7]. The Elia et al. (2018) Nature Communications publication reported the results of a five-week Phase 1/2 study in 30 adolescents aged 12 to 17 with ADHD and confirmed mGluR network gene variants. The study employed a single-blind, placebo-controlled design with an initial pharmacokinetic profiling phase (50 to 800 mg single dose) followed by four weeks of symptom-driven dose advancement up to 400 mg twice daily. Clinical Global Impressions Improvement (CGI-I) scores improved from 3.79 at baseline to 2.33 at week 5 (P less than 0.001), and Clinical Global Impressions Severity (CGI-S) scores improved from 4.83 to 3.86 (P less than 0.001). Parental Vanderbilt Assessment Scores showed significant improvement for subjects with Tier 1 mGluR network variants (P less than 0.035). No difference in adverse event incidence was observed between the placebo week and active treatment weeks [7].

Despite the initial pharmacogenomic signal, fasoracetam has not produced a registration-enabling efficacy demonstration in ADHD or any other indication. NeuroFix was acquired by Medgenics in 2015, which rebranded as Aevi Genomic Medicine in 2016 and subsequently became Avalo Therapeutics. Development of fasoracetam for ADHD was deprioritized. As of the most recent monograph revision, the compound is under Phase 2 investigation by Nobias Therapeutics for 22q11.2 deletion syndrome (DiGeorge syndrome), a genetic condition associated with cognitive deficits and psychiatric comorbidity [8].

The preclinical pharmacology of fasoracetam is more extensive than the clinical record. In rat models, the compound reverses scopolamine-induced amnesia in passive avoidance and radial arm maze paradigms at minimum effective doses of 0.1 mg/kg (active enantiomer), reverses baclofen-induced amnesia, increases in vivo acetylcholine release from the cerebral cortex, enhances high-affinity choline uptake in both cortex and hippocampus, reduces immobility time in the forced swimming test (an antidepressant-like effect comparable to desipramine), and reverses escape failure in the learned helplessness paradigm after repeated dosing [1, 2, 5, 9]. The learned helplessness reversal is accompanied by measurable upregulation of GABA-B receptor density in the cerebral cortex, a finding that distinguishes fasoracetam from other racetams and provides a mechanistic basis for the antidepressant-like behavioral profile [5].

The compound is not approved by any regulatory authority worldwide and is not marketed as a medicine. It is available as a research-grade preparation and has no established clinical dosing regimen for any indication. Investigators should confirm compound identity, chemical purity, and enantiomeric configuration on every research-grade lot.

3. Discovery and Development History

3.1 Origin

Fasoracetam was synthesized at Nippon Shinyaku Co., Ltd. in Kyoto, Japan, in the mid-1980s as part of a medicinal chemistry program exploring 5-substituted pyrrolidinone derivatives as cognition enhancers. The earliest patent application carries a priority date of January 21, 1986. The compound was identified from the series on the basis of potent anti-amnestic activity in rat scopolamine-challenge models, favorable oral bioavailability, and acceptable acute toxicity. It received the internal designation NS-105 [3, 6].

3.2 Preclinical development at Nippon Shinyaku

Through the late 1980s and 1990s, the Nippon Shinyaku pharmacology group published a series of studies characterizing the mechanism and behavioral pharmacology of NS-105. The principal publications are: Maeda et al. (1994, 1997) on acetylcholine release and high-affinity choline uptake enhancement in the cerebral cortex and hippocampus following NS-105 administration [1, 2]; Oguchi et al. (1998) on the reversal of learned helplessness and the accompanying GABA-B receptor upregulation in rat cerebral cortex after repeated dosing [5]; and Ito et al. (1999) on the involvement of both cholinergic and GABAergic systems in the reversal of memory disruption [9]. These studies established the triple-mechanism pharmacological profile that distinguishes fasoracetam from simpler racetams such as piracetam and aniracetam, which act predominantly through modulation of ionotropic glutamate receptors (AMPA receptor positive allosteric modulation in the case of aniracetam) without characterized GABA-B receptor activity.

3.3 Phase 3 trials for vascular dementia

Nippon Shinyaku advanced NS-105 through Phase 1, Phase 2, and Phase 3 clinical trials in Japan during the 1990s for the treatment of cognitive impairment associated with vascular dementia. Phase 2 and Phase 3 trials were multicenter, randomized, placebo-controlled studies evaluating doses of 100 to 800 mg daily. Primary endpoints were cognitive measures including the Alzheimer's Disease Assessment

Scale cognitive subscale (ADAS-cog) and clinical global impression scales. The Phase 3 program failed to demonstrate statistically significant improvement on cognitive endpoints relative to placebo. The total investment by Nippon Shinyaku in the fasoracetam development program reportedly exceeded 200 million United States dollars. The vascular dementia program was discontinued in the early 2000s [6, 10].

3.4 Acquisition and repurposing for ADHD

In approximately 2013, NeuroFix, Inc. was founded to acquire the Nippon Shinyaku fasoracetam clinical data package and to repurpose the compound for attention deficit hyperactivity disorder. The NeuroFix thesis was driven by genomic discoveries at the Center for Applied Genomics at the Children's Hospital of Philadelphia, where the laboratory of Hakon Hakonarson identified an enrichment of rare copy number variants and single nucleotide variants in genes encoding components of the metabotropic glutamate receptor signaling network in ADHD patient cohorts [7]. Fasoracetam, with its characterized mGluR modulation activity, was identified as a candidate therapeutic for the genetically defined ADHD subpopulation.

NeuroFix was acquired by Medgenics, Inc. in 2015. Medgenics rebranded as Aevi Genomic Medicine, Inc. in 2016 and initiated clinical trials of NFC-1 (fasoracetam) in adolescents with ADHD and confirmed mGluR network gene variants. The Phase 1/2 study results were published in Nature Communications in January 2018 [7]. Aevi was subsequently renamed Avalo Therapeutics, which deprioritized the ADHD indication following difficulties in demonstrating efficacy at larger scale.

3.5 Current development status

As of the most recent monograph revision, Nobias Therapeutics holds development rights for fasoracetam in 22q11.2 deletion syndrome (DiGeorge syndrome), a chromosomal microdeletion disorder associated with cognitive impairment, behavioral abnormalities, ADHD-like symptoms, and psychiatric comorbidity including elevated schizophrenia risk. A Phase 2 clinical trial for this indication was reported to be active as of 2023 [8]. No registration-enabling efficacy data have been published for fasoracetam in any indication.

4. Mechanism of Action

Fasoracetam is a multi-mechanism nootropic agent. Its principal molecular activities, characterized in rat in vivo and in vitro systems by the Nippon Shinyaku pharmacology group, are upregulation of GABA-B receptors in the cerebral cortex; modulation of metabotropic glutamate receptors; and facilitation of cholinergic neurotransmission through enhanced high-affinity choline uptake and increased acetylcholine release. These activities operate at functionally relevant concentrations achieved after oral administration and contribute differentially to the observed anti-amnesic, antidepressant-like, and procognitive effects in preclinical models.

4.1 GABA-B receptor upregulation

The gamma-aminobutyric acid type B (GABA-B) receptor is a heterodimeric G-protein-coupled receptor composed of GABA-B1 and GABA-B2 subunits, coupled to Gi/Go proteins. Activation produces inhibition of adenylyl cyclase, activation of inwardly rectifying potassium channels (GIRK channels), and inhibition of voltage-gated calcium channels, resulting in pre- and postsynaptic inhibition. GABA-B receptors are expressed throughout the central nervous system and play modulatory roles in cognition, mood, anxiety, and pain processing.

The Oguchi et al. (1998) study demonstrated that repeated administration of NS-105 (fasoracetam) to rats increased the number of GABA-B receptor binding sites (Bmax) in the cerebral cortex without altering the affinity (Kd) of the receptor for its radioligand [5]. This upregulation was observed after subchronic dosing (repeated daily administration over multiple days) but not after single acute doses. The GABA-B upregulation was specific; repeated NS-105 administration did not alter the binding properties of beta-adrenoceptors or 5-HT2 serotonin receptors in the same cortical preparations.

The functional consequence of GABA-B receptor upregulation by fasoracetam is complex. GABA-B agonists such as baclofen produce amnesia and cognitive impairment; fasoracetam reverses baclofen-induced amnesia in rat passive avoidance models [9]. The upregulation of GABA-B receptor density following repeated fasoracetam may represent a compensatory mechanism that restores or rebalances GABAergic inhibitory tone in circuits where GABA-B receptor expression has been

reduced by chronic stress, neurodegeneration, or pharmacological challenge. The reversal of learned helplessness (a rodent behavioral model of depression) following repeated fasoracetam dosing, accompanied by GABA-B upregulation, supports the interpretation that the GABA-B mechanism contributes to the antidepressant-like behavioral profile of the compound [5].

4.2 Metabotropic glutamate receptor modulation

Metabotropic glutamate receptors (mGluRs) are a family of eight G-protein-coupled receptors divided into three groups based on sequence homology, signal transduction, and pharmacological profile. Group I (mGluR1, mGluR5) are coupled to Gq/G11 and activate phospholipase C; Group II (mGluR2, mGluR3) and Group III (mGluR4, mGluR6, mGluR7, mGluR8) are coupled to Gi/Go and inhibit adenylyl cyclase. The mGluRs play essential roles in synaptic plasticity, learning, memory, and neurodevelopment.

Fasoracetam activates metabotropic glutamate receptors across all three groups [7, 11]. The precise binding site and mechanism of activation (direct agonism, positive allosteric modulation, or indirect facilitation through upstream signaling) have not been fully elucidated for each receptor subtype. The mGluR modulation was a central element of the pharmacogenomic stratification strategy employed in the Elia et al. (2018) ADHD clinical trial, in which enrolled adolescents carried confirmed mutations in genes encoding mGluR network components (including GRM1 through GRM8, GRIK1, GRIN2B, SLC1A2, SLC1A3, and associated signaling pathway genes) [7]. The hypothesis was that fasoracetam, as an mGluR activator, could compensate for the functional deficit in glutamatergic signaling produced by these genetic variants.

The mGluR modulation is mechanistically distinct from the AMPA receptor positive allosteric modulation attributed to aniracetam and from the non-specific membrane effects proposed for piracetam. It provides a rationale for the broader neuropsychiatric activity profile of fasoracetam (ADHD, mood, cognition) compared to simpler racetams whose activity is limited to cognitive enhancement in cholinergic deficit models.

4.3 Cholinergic facilitation

Fasoracetam enhances cholinergic neurotransmission through two characterized mechanisms: stimulation of high-affinity choline uptake (HACU) and increased acetylcholine release [1, 2].

High-affinity choline uptake is the rate-limiting step in acetylcholine biosynthesis. The choline transporter (CHT1, SLC5A7) at cholinergic nerve terminals captures extracellular choline for intracellular acetylation by choline acetyltransferase. NS-105 at 10 mg/kg enhanced HACU in both the cerebral cortex and hippocampus of rats with lesions of the nucleus basalis magnocellularis (a model of cholinergic deafferentation relevant to Alzheimer-type dementia) and in rats treated with pentobarbital (a model of pharmacological cholinergic suppression) [1, 2].

In parallel, NS-105 increased *in vivo* release of acetylcholine from the cerebral cortex as measured by microdialysis [2]. The acetylcholine release enhancement was observed at doses that also produced anti-amnestic effects in behavioral paradigms, supporting the interpretation that cholinergic facilitation is a functional contributor to the procognitive activity of the compound.

The cholinergic mechanism of fasoracetam is shared with coluracetam, another racetam that enhances HACU, but is distinct from the acetylcholinesterase inhibition mechanism of donepezil and rivastigmine. Fasoracetam does not inhibit acetylcholinesterase and does not directly bind nicotinic or muscarinic acetylcholine receptors at pharmacologically relevant concentrations [1, 9].

4.4 Receptor selectivity

Preclinical binding studies have demonstrated that NS-105 does not show affinity for adrenoceptors (alpha-1, alpha-2, beta), serotonergic receptors (5-HT₁, 5-HT₂), or dopaminergic receptors at concentrations up to 100 micromolar [5, 9]. The compound does not bind the GABA-A receptor or the benzodiazepine site. These selectivity data indicate that the behavioral effects of fasoracetam are mediated through the GABA-B, mGluR, and cholinergic mechanisms described above rather than through direct monoaminergic activity.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Fasoracetam is rapidly absorbed from the gastrointestinal tract after oral administration. In the Elia et al. (2018) Phase 1/2 study in adolescents, single-dose pharmacokinetic profiling across the 50 to 800 mg dose range demonstrated dose-proportional pharmacokinetics with time to peak plasma concentration (T_{max}) of 1.3 to 1.9 hours across all dose levels [7]. Oral bioavailability, characterized in preclinical (rat and dog) studies, ranges from 79 to 97 percent, indicating minimal first-pass metabolism [10, 12].

5.2 Distribution

Fasoracetam is a small, moderately lipophilic molecule (molecular weight 196.25, calculated logP approximately 0.5 to 1.0) that distributes readily to the central nervous system. Brain-to-plasma ratios in rodent studies indicate adequate central nervous system penetration for pharmacological effect. Plasma protein binding has not been reported in published form but is expected to be low to moderate based on the physicochemical properties of the compound and on the pharmacokinetic profile (rapid absorption, renal excretion of unchanged drug).

5.3 Metabolism

Fasoracetam undergoes minimal hepatic metabolism. The compound is a stable lactam amide that resists hydrolysis and oxidative biotransformation under physiological conditions. Unlike tropisetron and many other centrally active agents, fasoracetam is not a substrate for cytochrome P450 enzymes at pharmacologically relevant concentrations [7, 12]. There is little, if any, enterohepatic circulation. The absence of significant hepatic metabolism implies minimal potential for metabolic drug-drug interactions and eliminates CYP polymorphism as a variable in dose-response, a substantial simplification relative to compounds where CYP phenotype is a dominant pharmacokinetic determinant.

5.4 Elimination

Fasoracetam is excreted predominantly unchanged through the kidneys. Renal clearance is the principal elimination pathway. The plasma elimination half-life across the dose range studied in the Elia et al. (2018) adolescent ADHD trial ranged from 4.06 to 6.99 hours, with an average of approximately 4.8 hours [7]. The half-life is dose-independent within the studied range, consistent with linear pharmacokinetics and first-order elimination.

Renal impairment would be expected to prolong the elimination half-life and increase drug exposure. Hepatic impairment is not expected to materially affect pharmacokinetics given the minimal hepatic metabolism.

5.5 Routes of administration

The primary route of administration in both the Japanese vascular dementia trials and the ADHD clinical program was oral. The compound has been administered intraperitoneally in rodent preclinical studies at doses of 0.1 to 100 mg/kg. Intravenous administration has been used in preclinical pharmacokinetic studies for bioavailability determination. No parenteral formulation has been developed for human clinical use.

5.6 Special populations

Pharmacokinetic data in the Elia et al. (2018) study were obtained in adolescents aged 12 to 17 years [7]. Adult pharmacokinetic data from the Nippon Shinyaku Phase 1 program have not been published in detail in the English-language literature. Pediatric, geriatric, and renally or hepatically impaired population pharmacokinetic data are not available in published form. Given the renal elimination pathway, dose adjustment in renal impairment would be prudent for investigational use.

6. Preclinical Pharmacology

6.1 Anti-amnestic activity

The foundational preclinical characterization of NS-105 established anti-amnestic efficacy across multiple rodent models of cholinergic and GABAergic dysfunction [1, 2, 9].

Scopolamine-induced amnesia: NS-105 reversed the memory disruption produced by the muscarinic antagonist scopolamine in both passive avoidance and radial arm maze paradigms in rats. The minimum effective dose for the active (5R) enantiomer was 0.1 mg/kg intraperitoneally, approximately 10-fold more potent than the racemic mixture, confirming the stereoselectivity of the anti-amnestic effect [3].

Baclofen-induced amnesia: The GABA-B agonist baclofen produces dose-dependent amnesia through presynaptic inhibition of neurotransmitter release. NS-105 reversed baclofen-induced amnesia in passive avoidance, supporting the functional relevance of the GABA-B receptor mechanism [9].

Electric shock and carbon dioxide-induced amnesia: NS-105 reversed amnesia produced by electroconvulsive shock and by carbon dioxide inhalation in rat passive avoidance models [3].

Nucleus basalis magnocellularis lesion model: In rats with ibotenic acid lesions of the nucleus basalis magnocellularis (a model of cholinergic basal forebrain degeneration analogous to that observed in Alzheimer's disease and vascular dementia), NS-105 enhanced high-affinity choline uptake and partially restored cognitive performance [1, 2].

6.2 Antidepressant-like activity

NS-105 demonstrated antidepressant-like activity in two standard rodent behavioral models [5].

Forced swimming test: NS-105 at doses of 1 to 100 mg/kg orally produced dose-dependent reduction in immobility time, an effect comparable in magnitude to that of the tricyclic antidepressant desipramine [5].

Learned helplessness paradigm: Rats exposed to inescapable footshock develop a failure-to-escape phenotype when subsequently placed in a shuttle box with an available escape response. Repeated administration of NS-105 reversed this escape failure, an effect that was accompanied by the GABA-B receptor upregulation measured in cortical membrane binding assays [5]. Single-dose administration did not reverse learned helplessness, indicating that the antidepressant-like effect requires the subchronic GABA-B receptor adaptation.

6.3 Cholinergic enhancement in vivo

Microdialysis studies demonstrated that NS-105 at 10 mg/kg increased extracellular acetylcholine concentrations in the cerebral cortex of freely moving rats [2]. The enhancement was observed in both intact animals and in animals with basal fore-brain lesions, suggesting that the mechanism involves potentiation of residual cholinergic function rather than direct receptor activation. The HACU enhancement in cortex and hippocampus was confirmed in ex vivo synaptosomal preparations [1].

6.4 Toxicology

Acute toxicity studies in rodents reported by Nippon Shinyaku indicate that the oral LD50 of fasoracetam exceeds 5000 mg/kg in both mice and rats, placing the compound in a low acute toxicity category consistent with other racetams [10]. Subchronic (28-day) and chronic (6-month) repeated-dose toxicity studies in rats and dogs at doses up to 1000 mg/kg/day were completed as part of the Japanese regulatory package; detailed published results are not available in the English-language literature, but the compound advanced to Phase 3 clinical trials, indicating acceptable preclinical safety.

7. Clinical Evidence Base

7.1 Vascular dementia (Nippon Shinyaku program)

The Nippon Shinyaku clinical program for vascular dementia comprised Phase 1 healthy volunteer pharmacokinetic studies, Phase 2 dose-finding studies, and Phase 3 pivotal efficacy trials conducted in Japan during the 1990s [6, 10]. Doses ranged from 100 to 800 mg daily. Phase 3 trials were multicenter, randomized, double-blind, placebo-controlled studies evaluating cognitive endpoints including the ADAS-cog. The trials failed to demonstrate statistically significant improvement on primary cognitive endpoints relative to placebo. The magnitude of the cognitive deficit in vascular dementia populations, the heterogeneity of vascular dementia etiology, and the dose range studied may have contributed to the negative result. Detailed trial data have not been published in the English-language peer-reviewed literature, and the available information derives from regulatory filings, conference abstracts, and the AdisInsight drug development record [6, 10].

7.2 ADHD with mGluR gene variants (Elia et al. 2018)

The Elia et al. (2018) study published in Nature Communications is the principal published human clinical study of fasoracetam [7]. This five-week, open-label, single-blind, placebo-controlled Phase 1/2 study enrolled 30 adolescents aged 12 to 17 years with DSM-5-diagnosed ADHD who also carried confirmed mutations in genes of the mGluR signaling network, identified through whole-exome sequencing and copy number variant analysis.

Study design: The study began with single-dose pharmacokinetic profiling at doses from 50 to 800 mg, followed by one week of single-blind placebo, then four weeks of active treatment with symptom-driven dose advancement up to 400 mg twice daily.

Primary endpoints: Safety, tolerability, and pharmacokinetics. Secondary endpoints included Clinical Global Impressions Improvement (CGI-I), Clinical Global Impressions Severity (CGI-S), and parental Vanderbilt ADHD Assessment Scores.

Results: Mean CGI-I scores improved from 3.79 at baseline to 2.33 at week 5 (P less than 0.001). Mean CGI-S scores improved from 4.83 at baseline to 3.86 at week 5 (P less than 0.001). Parental Vanderbilt scores showed significant improvement for subjects with Tier 1 mGluR network variants (P less than 0.035). The pharmacogenomic stratification identified a gradient of response: subjects with the most functionally disruptive mGluR gene variants (Tier 1) showed the greatest clinical improvement.

Safety: There were no statistically significant differences in the incidence of adverse events between the placebo week and the active treatment weeks. Reported adverse events were mild and included headache, fatigue, and gastrointestinal discomfort. No serious adverse events were reported.

Limitations: The study was small (n=30), open-label after the first week, lacked a concurrent placebo control arm for the full treatment period, and enrolled only adolescents with a specific genetic profile. The results demonstrate safety and pharmacokinetic feasibility and provide a pharmacogenomic efficacy signal, but do not constitute registration-enabling evidence of efficacy.

7.3 22q11.2 deletion syndrome (Nobias Therapeutics)

Nobias Therapeutics has advanced fasoracetam into Phase 2 investigation for cognitive and behavioral symptoms associated with 22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome) [8]. The 22q11.2 deletion removes approximately 1.5 to 3 megabases from chromosome 22q11.2 and is associated with congenital heart disease, palatal abnormalities, immune deficiency, cognitive impairment, and a markedly elevated risk of psychiatric disorders including schizophrenia, ADHD, and anxiety. The glutamatergic signaling dysfunction in 22q11.2 deletion syndrome provides a mechanistic rationale for mGluR-modulating therapy. Published clinical data from this program are not yet available.

7.4 Other investigated indications

Early Nippon Shinyaku publications reference investigation of NS-105 for broader cognitive decline, post-stroke cognitive impairment, and age-related memory impairment [6, 10]. None of these indications advanced beyond exploratory clinical stages, and no published efficacy data are available.

8. Sourcing and Quality Verification

Fasoracetam is not marketed as a registered medicine in any jurisdiction. No pharmaceutical-grade product (with regulatory-approved manufacturing, formulation, and release specifications) is commercially available.

Research-grade fasoracetam is supplied by multiple chemical research suppliers (Sigma-Aldrich, Cayman Chemical, MedChemExpress, MedKoo Biosciences, BOC Sciences, Tocris, and others) at stated purities of greater than 98 percent by HPLC. Supply is in milligram to gram quantities as the free base. Pricing is moderate, typically in the range of \$30 to \$150 per gram at research scale.

Fasoracetam is also sold in the unregulated nootropic market as a dietary supplement or research chemical, often in capsule or powder form. The quality, purity, and enantiomeric configuration of these products are variable and unverified. Investigators should not rely on vendor certificates of analysis from nootropic retailers without independent analytical confirmation.

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

- High-performance liquid chromatography area-percent purity (greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (197.13 for the protonated molecule $[M+H]^+$)
- Chiral HPLC or optical rotation confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (5R) form), as the (5S) enantiomer has substantially reduced activity and the racemic mixture would confound dose-response investigations
- Nuclear magnetic resonance spectroscopy for structural confirmation (1H and ^{13}C NMR)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, and others) provide independent confirmation of vendor certificates of analysis. Given the absence of pharmaceutical-grade material and the variability of the unregulated market, independent analytical verification is essential for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Fasoracetam is supplied as a white to off-white crystalline powder that is freely soluble in water at room temperature. For research applications, the compound can be prepared as aqueous stock solutions at concentrations of 10 to 100 mg/mL in normal saline, in phosphate-buffered saline, or in bacteriostatic water for injection for parenteral research applications.

For in vitro studies requiring higher concentrations, the compound dissolves readily in dimethyl sulfoxide (DMSO) at concentrations exceeding 100 mM (approximately 20 mg/mL). Aliquot DMSO stock solutions in single-use volumes and store at minus 20 degrees Celsius to avoid repeated freeze-thaw degradation.

Storage of the solid material is appropriate at room temperature (15 to 25 degrees Celsius) in a dry, light-protected environment. The compound is chemically stable under ambient conditions; the lactam ring is resistant to hydrolysis and the amide bond is stable under physiological pH. Desiccant is recommended for long-term storage to prevent hygroscopic moisture uptake.

Aqueous solutions prepared for in vivo research should be used within 7 to 14 days when stored at 2 to 8 degrees Celsius, or within 24 hours at room temperature if prepared in sterile water without preservative. Solutions prepared in bacteriostatic water (0.9 percent benzyl alcohol) are stable for up to 30 days at 2 to 8 degrees Celsius, consistent with standard reconstitution practices.

For oral administration in rodent preclinical studies, fasoracetam is typically dissolved directly in the dosing vehicle (water, 0.5 percent methylcellulose, or normal saline) immediately before gavage. The compound does not require pH adjustment for dissolution.

10. Stack Interactions and Combinations

Fasoracetam interacts with several drug classes through its GABA-B, mGluR, and cholinergic mechanisms. Investigators conducting research with fasoracetam, especially in chronic dosing regimens or in combination with other research compounds, should consider:

GABA-B agonists and positive allosteric modulators: Baclofen and other GABA-B agonists produce amnesia and sedation that fasoracetam can reverse in preclinical models [9]. The pharmacological interaction is functionally antagonistic at the behavioral level, though the mechanism (GABA-B receptor upregulation by fasoracetam versus direct receptor activation by baclofen) is indirect. Phenibut, a GABA-B agonist commonly used in the nootropic community, has been reported in a case report of combined overdose with fasoracetam [13]. The combination of fasoracetam with GABA-B agonists is pharmacologically complex and unpredictable at supratherapeutic doses.

Cholinergic agents: Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) produce additive cholinergic enhancement when combined with fasoracetam. The combination is pharmacologically rational for cognitive applications but may amplify cholinergic adverse events (nausea, diarrhea, salivation) at higher doses. Choline supplements (alpha-GPC, CDP-choline) are commonly co-administered with racetams in nootropic practice; the HACU-enhancing mechanism of fasoracetam provides a specific rationale for this combination, as enhanced choline uptake depends on choline substrate availability.

Other racetams: Concurrent administration with piracetam, aniracetam, pramiracetam, or other racetams is common in nootropic practice but has not been studied in controlled preclinical or clinical research. The mechanisms are partially overlapping (cholinergic facilitation) and partially distinct (GABA-B upregulation is specific to fasoracetam; AMPA receptor modulation is more characteristic of aniracetam). Additive or synergistic effects are plausible but uncharacterized.

Stimulants: Concurrent administration with methylphenidate, amphetamine, or modafinil has not been studied. Fasoracetam does not bind dopaminergic or adrenergic receptors and is not expected to produce pharmacokinetic interactions given its minimal hepatic metabolism. Pharmacodynamic interactions (additive cognitive enhancement, potentially additive cardiovascular effects) are possible but uncharacterized.

Benzodiazepines and GABA-A modulators: Fasoracetam does not bind the GABA-A receptor or the benzodiazepine site. No direct pharmacokinetic or pharmacodynamic interaction is expected, though the GABA-B upregulation may indirectly modulate GABAergic tone in circuits where GABA-A and GABA-B receptors co-localize.

Anticonvulsants: The mGluR modulation by fasoracetam has theoretical relevance to anticonvulsant pharmacology, as mGluR Group II and Group III agonism can modulate seizure threshold. The interaction with anticonvulsant agents has not been studied.

CYP-metabolized drugs: Fasoracetam undergoes minimal hepatic metabolism and is not a substrate, inhibitor, or inducer of major CYP enzymes at pharmacologically relevant concentrations [7, 12]. Pharmacokinetic drug-drug interactions through CYP-mediated mechanisms are not expected.

11. Adverse Events and Safety

11.1 Clinical safety data

The clinical safety dataset for fasoracetam is limited. The two principal sources are the unpublished Nippon Shinyaku Phase 1 through Phase 3 program (involving several hundred Japanese patients with vascular dementia at doses of 100 to 800 mg daily) and the Elia et al. (2018) Phase 1/2 study (30 adolescents with ADHD at doses of 50 to 800 mg) [7].

In the Elia et al. (2018) study, there were no statistically significant differences in adverse event incidence between the single-blind placebo week and the four weeks of active treatment. Reported adverse events were mild and included:

- Headache
- Fatigue
- Gastrointestinal discomfort (nausea, abdominal pain)
- Dizziness
- Insomnia or somnolence

No serious adverse events were reported. No clinically significant changes in vital signs, electrocardiographic parameters, or laboratory values were observed.

11.2 Preclinical safety

The oral LD₅₀ in rodents exceeds 5000 mg/kg, indicating low acute toxicity [10]. Subchronic and chronic repeated-dose toxicity studies were completed as part of the Nippon Shinyaku regulatory package and supported advancement to Phase 3 clinical trials. Detailed toxicology findings are not available in the English-language published literature.

The racetam class as a whole has a favorable safety profile. Piracetam, the progenitor racetam, has been in clinical use for over 50 years with an extremely wide therapeutic index and minimal serious adverse event signal. The structural similarity of fasoracetam to other racetams and its low acute toxicity are consistent with

this class-wide safety profile, though the GABA-B receptor mechanism introduces a theoretical concern for interactions with GABAergic agents that is not shared by simpler racetams.

11.3 Limitations of the safety dataset

The clinical safety dataset for fasoracetam is insufficient to characterize rare adverse events, long-term effects of chronic administration, effects in special populations (elderly, renally impaired, pregnant or lactating), or interactions with commonly co-administered medications. The compound has not been subjected to the postmarketing pharmacovigilance that accompanies regulatory approval. Investigators should treat fasoracetam as an incompletely characterized investigational compound and should implement appropriate safety monitoring in any research application.

11.4 Case reports

A published case report described a combined overdose of phenibut and fasoracetam in a young adult, with clinical presentation dominated by phenibut toxicity (altered consciousness, respiratory depression) [13]. The contribution of fasoracetam to the clinical presentation was indeterminate. The case highlights the risk of uncontrolled self-experimentation with unregulated nootropic compounds.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five racetam and racetam-adjacent nootropic compounds against fasoracetam, 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 as the principal racetam-class or mechanistically related nootropics with substantive preclinical or clinical evidence bases, with priority on those that share aspects of fasoracetam's pharmacological profile or compete for the same research-clinical applications.

12.1 Piracetam

Mechanism: The progenitor racetam. Mechanism incompletely characterized after over 50 years of research. Proposed mechanisms include positive allosteric modulation of AMPA-type ionotropic glutamate receptors, modulation of membrane fluidity, enhancement of neurovascular coupling, and non-specific facilitation of cholinergic and glutamatergic transmission. Piracetam does not upregulate GABA-B receptors and does not modulate mGluRs at pharmacologically relevant concentrations [14, 15].

Development trajectory: Piracetam was synthesized by UCB Pharma in Belgium in 1964 and registered in multiple jurisdictions (not including the United States) for cognitive impairment, myoclonus, and vertigo. It has been in clinical use for over 50 years. It is the most extensively studied nootropic compound in the world, with thousands of published clinical and preclinical studies [14].

Novelty: Low. Piracetam defines the racetam class and is the reference compound. Its mechanism is non-specific and its effect size is modest.

Effect size: Small. Meta-analyses of piracetam in age-related cognitive decline and dementia report statistically significant but clinically modest improvements on global cognitive function scales, with effect sizes (Cohen's d) of approximately 0.2 to 0.3 [15]. Effect in healthy young adults is minimal or absent.

Promising potential: Low for new indications. The compound is a mature generic medicine with no active development programs. It remains the default comparator for racetam-class research.

Side-effect profile: Excellent. Piracetam has an extremely wide therapeutic index (oral LD50 in rodents exceeds 10,000 mg/kg). Clinical adverse events at registered doses (2.4 to 4.8 g daily) are infrequent and mild: insomnia, gastrointestinal discomfort, weight gain, agitation. No serious adverse event signal has been identified in over 50 years of postmarketing surveillance.

Overall validation: Moderate. Extensive clinical use and literature but limited large-scale, high-quality trials by modern regulatory standards. The compound was registered in an era of less rigorous trial methodology.

Comparison to fasoracetam: Piracetam is mechanistically simpler (no GABA-B upregulation, no mGluR modulation) and has a weaker effect size in preclinical cognitive models. Fasoracetam has a more targeted mechanism and produces anti-amnesic effects at doses approximately 10- to 100-fold lower than piracetam in comparable rodent models. Piracetam has the advantages of 50 years of clinical safety data, registered indications in multiple jurisdictions, and universal availability.

12.2 Aniracetam

Mechanism: Positive allosteric modulator of AMPA-type ionotropic glutamate receptors; modulator of metabotropic glutamate receptors (partial overlap with fasoracetam); anxiolytic activity attributed to indirect modulation of dopaminergic and serotonergic transmission. Aniracetam does not upregulate GABA-B receptors [16].

Development trajectory: Synthesized by Hoffmann-La Roche in the 1970s. Registered in Japan and in some European jurisdictions for cognitive impairment associated with cerebrovascular disease. Not approved in the United States.

Novelty: Low to moderate. The AMPA receptor positive allosteric modulation mechanism was novel at the time of characterization and has since been the basis for the ampakine class of cognition enhancers.

Effect size: Modest in clinical use. Preclinical effect sizes on anxiolytic and cognitive endpoints are moderate. Clinical trials in Alzheimer's disease and vascular dementia produced inconsistent results.

Promising potential: Low. The compound is a mature generic with no active development programs beyond its existing registrations.

Side-effect profile: Good. Aniracetam is well tolerated at clinical doses (1.5 g daily). Adverse events include gastrointestinal discomfort, headache, anxiety, and insomnia, all at low incidence.

Overall validation: Moderate. Registered in Japan and some European countries. Clinical evidence base is larger than fasoracetam but smaller than piracetam.

Comparison to fasoracetam: Aniracetam shares partial mGluR modulation with fasoracetam but differs in AMPA receptor positive allosteric modulation (characteristic of aniracetam) versus GABA-B receptor upregulation (characteristic of fasoracetam). Aniracetam has a stronger anxiolytic profile; fasoracetam has a stronger antidepressant-like profile in preclinical models. Aniracetam has the advantage of registered clinical indications; fasoracetam has the advantage of a more targeted and better-characterized mechanism.

12.3 Coluracetam (MKC-231)

Mechanism: Selective high-affinity choline uptake enhancer. Coluracetam is the most mechanistically focused racetam for cholinergic facilitation through the HACU mechanism, sharing this specific activity with fasoracetam [17]. It does not upregulate GABA-B receptors and has not been characterized as an mGluR modulator.

Development trajectory: Synthesized by Mitsubishi Tanabe Pharma in Japan. Advanced to Phase 2 clinical trials for major depressive disorder and generalized anxiety disorder by BrainCells, Inc. (licensed from Mitsubishi). Phase 2 results were mixed, and the compound was not advanced to Phase 3 [17].

Novelty: Moderate. The HACU enhancement mechanism is the most selective of any racetam and provides the clearest mechanistic link between racetam pharmacology and cholinergic facilitation.

Effect size: Mixed. Phase 2 results in depression showed a signal in a subset of patients (treatment-resistant depression) but did not meet primary endpoints in the overall population.

Promising potential: Low. Development has been discontinued. The compound is available as a research chemical.

Side-effect profile: Acceptable in Phase 2. Adverse events were mild and comparable to placebo.

Overall validation: Low to moderate. Phase 2 clinical data exist but are limited and did not support registration.

Comparison to fasoracetam: Coluracetam and fasoracetam share the HACU enhancement mechanism, making them the two racetams with the most specific cholinergic facilitation profile. Fasoracetam has additional GABA-B upregulation and mGluR modulation that coluracetam lacks, producing a broader pharmacological profile. Coluracetam has more advanced clinical depression data; fasoracetam has more advanced clinical ADHD data.

12.4 Phenylpiracetam (Fonturacetam)

Mechanism: Piracetam with a phenyl group appended to the pyrrolidinone ring, conferring enhanced lipophilicity, higher central nervous system penetration, and stimulant-like activity. The mechanism includes AMPA receptor modulation (shared with piracetam), dopamine reuptake inhibition, and increased locomotor activity. Phenylpiracetam does not upregulate GABA-B receptors and has not been characterized as an mGluR modulator [18].

Development trajectory: Synthesized by Soviet researchers in 1983 for cosmonauts. Registered in Russia and some Eastern European countries as Phenotropil for cognitive enhancement and asthenia. Listed as a prohibited substance by the World Anti-Doping Agency (WADA) as a non-specific stimulant. Not approved in the United States or Western Europe.

Novelty: Low to moderate. The phenyl group addition to piracetam is a straightforward structural modification. The stimulant mechanism is an addition to, rather than a refinement of, the piracetam pharmacology.

Effect size: Moderate for stimulant and physical performance endpoints. Cognitive effect sizes are modest in the limited published literature.

Promising potential: Low. No active Western development programs. The WADA ban limits sport-related research applications.

Side-effect profile: Moderate. The stimulant activity produces insomnia, agitation, and cardiovascular effects (elevated heart rate, blood pressure) that are not characteristic of other racetams. The stimulant profile limits chronic dosing.

Overall validation: Low to moderate. Registered in Russia with limited published English-language clinical data. The WADA ban provides indirect evidence of a genuine pharmacological effect.

Comparison to fasoracetam: Phenylpiracetam and fasoracetam occupy opposite poles of the racetam spectrum. Phenylpiracetam is stimulatory and dopaminergic; fasoracetam is non-stimulatory and GABAergic/glutamatergic. The two compounds have no pharmacological overlap beyond the shared pyrrolidinone core. Investigators seeking a non-stimulant cognitive enhancer would favor fasoracetam; those seeking a psychostimulant nootropic would favor phenylpiracetam.

12.5 Pramiracetam

Mechanism: High-affinity choline uptake enhancer and glutamatergic modulator. Pramiracetam is structurally derived from piracetam with a dipropan-2-ylamino ethyl amide side chain. It enhances HACU (shared with fasoracetam and coluracetam) and is reported to increase nitric oxide synthase activity in the hippocampus. It does not upregulate GABA-B receptors [19].

Development trajectory: Synthesized by Parke-Davis in the 1970s. Registered in Italy and some Eastern European countries for cognitive impairment. Phase 2 clinical data exist for traumatic brain injury cognitive rehabilitation. Not approved in the United States.

Novelty: Low. The mechanism is a refinement of the piracetam pharmacology with enhanced potency but not a fundamentally different approach.

Effect size: Moderate in preclinical models of cognitive impairment. Clinical data are limited; a small study in traumatic brain injury showed cognitive improvement, and a study in elderly subjects showed memory enhancement [19].

Promising potential: Low. No active development programs beyond existing registrations.

Side-effect profile: Good. Pramiracetam is well tolerated at clinical doses (600 to 1200 mg daily). Adverse events are infrequent and mild.

Overall validation: Low to moderate. Registered in some European countries with limited published clinical data.

Comparison to fasoracetam: Pramiracetam and fasoracetam share the HACU enhancement mechanism. Fasoracetam has additional GABA-B upregulation and mGluR modulation. Pramiracetam has the advantage of registered clinical indications and a longer clinical track record; fasoracetam has the advantage of a more diverse and better-characterized mechanism and more recent clinical data (the Elia et al. 2018 pharmacogenomic ADHD study).

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the racetam and nootropic pharmacology space. **Piracetam** is the progenitor compound with the largest safety dataset but the smallest effect size and the least specific mechanism. **Aniracetam** adds AMPA receptor positive allosteric modulation and anxiolytic activity. **Coluracetam** provides the most selective HACU enhancement. **Phenylpiracetam** adds stimulant and dopaminergic activity. **Pramiracetam** offers enhanced potency with HACU facilitation and a clinical track record in cognitive rehabilitation.

Fasoracetam occupies a unique position in this landscape: it is the only racetam with characterized GABA-B receptor upregulation, the only racetam with confirmed activity across all three mGluR groups, and the only racetam that has been investigated using a pharmacogenomic stratification strategy in a published clinical trial. Its triple-mechanism profile (GABA-B upregulation, mGluR modulation, cholinergic facilitation) is the most mechanistically diverse of the racetam class and provides the broadest potential therapeutic scope, spanning cognition, mood (antidepressant-like activity), and the genetically defined ADHD subpopulation with mGluR network dysfunction.

The principal limitation of fasoracetam relative to the comparators is clinical validation. It is the only compound in this panel with no registered indication in any jurisdiction. The Phase 3 vascular dementia failure and the disappointing ADHD efficacy at scale are significant liabilities. The current Phase 2 investigation in 22q11.2 deletion syndrome represents a mechanistically rational application, but published clinical data are not yet available.

Investigators considering fasoracetam for research applications should weight the mechanistic novelty and pharmacogenomic rationale against the absence of clinical registration, the limited human safety dataset, and the developmental trajectory marked by negative efficacy results in the vascular dementia and broader ADHD indications. The compound's greatest research value is as a mechanistic tool for studying GABA-B receptor plasticity, mGluR-mediated cognition, and cholinergic facilitation in genetically stratified populations, rather than as a clinically validated therapeutic.

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