

RESEARCH MONOGRAPH . COMPOUND PROFILE

Esmethadone

The (S)-enantiomer of racemic methadone, developed by Relmada Therapeutics as REL-1017 for major depressive disorder on the basis of low-potency, voltage-dependent uncompetitive NMDA receptor channel blockade with preferential tonic inhibition of GluN2D-containing receptors, negligible clinically relevant opioid agonist activity, and rapid mTORC1- and BDNF-dependent antidepressant-like effects in preclinical models.

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ABSTRACT

Esmethadone (REL-1017, d-methadone, dextromethadone) is the (S)-enantiomer of the synthetic opioid methadone and a low-potency, voltage-dependent, uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor that was advanced through Phase 3 clinical development by Relmada Therapeutics for the adjunctive and monotherapy treatment of major depressive disorder (MDD). Unlike the (R)-enantiomer levomethadone, which carries the analgesic opioid activity of the racemate, esmethadone exhibits approximately 10-fold lower affinity at mu-opioid receptors and lacks clinically meaningful opioid agonist effects, respiratory depression, reinforcing properties, or physical dependence liability at the doses studied for antidepressant activity. The compound blocks NMDA receptor ion channels with IC₅₀ values in the low micromolar range (approximately 13 to 68 micromolar across GluN2A through GluN2D subunit combinations), with functional selectivity for tonically active GluN2D-containing receptors under physiological magnesium concentrations. This tonic blockade is proposed to disinhibit downstream alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated glutamatergic transmission, activate mammalian target of rapamycin complex 1 (mTORC1) signaling, and increase brain-derived neurotrophic factor (BDNF) expression, producing rapid-onset antidepressant effects comparable in mechanism (though not in potency or dissociative liability) to ketamine and esketamine. Preclinical studies in rodent models of depressive-like behavior (forced swimming test, novelty-suppressed feeding test, female urine sniffing test, chronic unpredictable stress) demonstrated that oral

esmethadone produced antidepressant effects comparable to injectable ketamine in magnitude and duration, mediated by mTORC1 signaling in the medial prefrontal cortex and blocked by the selective mTORC1 inhibitor rapamycin. A Phase 1 study in healthy volunteers demonstrated that esmethadone increased circulating BDNF levels, providing translational biomarker support for the preclinical mechanism. Pharmacokinetics are characterized by approximately 70 to 80 percent oral bioavailability, a long elimination half-life exceeding 30 hours that supports once-daily dosing, and hepatic metabolism principally through CYP3A4/5 and CYP2B6 to the inactive metabolite EDDP, with approximately half the dose recovered in urine and 40 percent in feces. The compound is a CYP2D6 inhibitor in vitro, producing clinically relevant increases in exposure of CYP2D6 substrates such as dextromethorphan. The Phase 2a randomized, double-blind, placebo-controlled adjunctive trial in MDD patients with inadequate response to standard antidepressants (Fava et al., *American Journal of Psychiatry*, 2022) demonstrated rapid and sustained improvement on the Montgomery-Asberg Depression Rating Scale (MADRS) at 25 mg and 50 mg daily doses, with effect sizes of 0.7 to 1.0 and day-14 remission rates of 31 percent and 39 percent versus 5 percent on placebo. No dissociative or psychotomimetic effects were observed. The Phase 3 Reliance I trial (published 2024) did not meet its primary efficacy endpoint, attributed in part to an elevated placebo response during the COVID-19 pandemic enrollment period. A second Phase 3 trial (Reliance II) was initiated, but interim analysis in late 2024 indicated that the study was unlikely to meet its primary efficacy endpoint, and Relmada Therapeutics paused further development of REL-1017. A 12-month open-label extension study in 624 MDD patients confirmed long-term safety and tolerability, with the

most common treatment-related adverse events being headache (4.6 percent), nausea (4.2 percent), and dizziness (2.6 percent), no signal for cardiovascular, metabolic, neurological, or sexual adverse events, no suicides or suicide attempts, and no withdrawal syndrome on discontinuation. A dedicated abuse-potential study in recreational drug users demonstrated no meaningful abuse potential. The compound is not approved by any regulatory authority. This monograph reviews the chemistry, stereochemistry, and synthesis of esmethadone; the NMDA receptor pharmacology including subunit selectivity and downstream signaling; the opioid receptor binding profile; comprehensive pharmacokinetics including drug-drug interactions; the preclinical and clinical evidence base across Phase 1, Phase 2, and Phase 3 programs; sourcing and quality considerations; reconstitution and handling; stack interactions; the adverse-event and safety profile; and a comparative assessment of five alternative NMDA receptor-targeting antidepressant candidates against esmethadone on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Esmethadone.

Other names: Dextromethadone, d-methadone, (S)-methadone, (+)-methadone. The naming convention reflects the dextrorotatory optical activity of the (S)-enantiomer; the compound rotates plane-polarized light to the right. The prefix "es-" in the INN follows the convention for the (S)-enantiomer (analogous to esketamine, escitalopram, esomeprazole).

Development codes: REL-1017 (Relmada Therapeutics). SPN-820 was used in some preclinical publications referring to the same chemical entity. The development code REL-1017 is the canonical identifier in the clinical literature and on ClinicalTrials.gov registrations.

Chemical Abstracts Service registry numbers: 5653-80-5 (free base). The hydrochloride salt (esmethadone hydrochloride) is registered in PubChem under compound identifier CID 20055402. Racemic methadone is registered under CAS 76-99-3; the (R)-enantiomer levomethadone under CAS 125-58-6.

International Union of Pure and Applied Chemistry name: (S)-6-(dimethylamino)-4,4-diphenylheptan-3-one. The compound is the (S)-configured enantiomer at the sole stereocenter (carbon-6) of the 6-(dimethylamino)-4,4-diphenylheptan-3-one scaffold.

1.2 Structural class and chemistry

Esmethadone is a synthetic diphenylheptanone derivative. The structural class is the methadone family, characterized by two phenyl groups attached to carbon-4, a propionyl ketone at carbon-3, and a dimethylamino group at carbon-6. The class was originally developed in Germany during the Second World War at Hoechst AG (then I.G. Farbenindustrie) by Max Bockmuehl and Gustav Ehrhart, who synthesized racemic methadone in 1937 as an analgesic candidate [1]. The racemate was subsequently separated into its component enantiomers; the (R)-enantiomer (lev-

omethadone) carries essentially all of the mu-opioid receptor agonist activity, while the (S)-enantiomer (esmethadone) retains the NMDA receptor antagonist activity with substantially reduced opioid potency.

Molecular formula: C₂₁H₂₇NO (free base); C₂₁H₂₈ClNO (hydrochloride salt).

Exact mass: 309.2093 g/mol (free base, monoisotopic).

Molecular weight: 309.45 g/mol (free base); 345.91 g/mol (hydrochloride salt).

Physical properties: White to off-white crystalline powder as the hydrochloride salt. Freely soluble in water, methanol, and ethanol; soluble in chloroform; sparingly soluble in diethyl ether. The free base is an oil at room temperature. Melting point of the hydrochloride salt is approximately 235 to 237 degrees Celsius.

Stereochemistry: Esmethadone contains a single stereocenter at carbon-6 and is supplied as the pure (S)-enantiomer. The absolute configuration was assigned by Bockmuehl's original resolution and confirmed by X-ray crystallography and by optical rotation measurements. The specific optical rotation ($[\alpha]_D$) is positive (dextrorotatory), distinguishing it from the levorotatory (R)-enantiomer. Investigators acquiring esmethadone should confirm enantiomeric purity by chiral high-performance liquid chromatography or chiral gas chromatography, as contamination with the (R)-enantiomer would introduce opioid agonist activity.

1.3 Synthesis

The synthesis of esmethadone historically proceeded through resolution of racemic methadone, which is itself prepared by a convergent route: condensation of diphenylacetonitrile with 2-chloro-1-(dimethylamino)propane (or the equivalent 1-dimethylamino-2-propyl chloride) under strong base to form the quaternary carbon, followed by addition of ethylmagnesium bromide (Grignard reaction) to the nitrile and acid hydrolysis to the ketone [1, 2]. Resolution of the racemate was traditionally achieved by diastereomeric salt formation with chiral acids (d-tartaric acid, dibenzoyl-d-tartaric acid) followed by fractional recrystallization [2].

More recent asymmetric synthesis methods include lipase-catalyzed kinetic resolution of racemic methadone intermediates and a chiral pool approach based on cyclic sulfamidate ring-opening reaction, which provides access to enantiomerically pure (R)- and (S)-methadone with high enantiomeric excess [3]. Industrial-scale production for the REL-1017 clinical program employed a proprietary manu-

facturing process optimized for enantiomeric purity (greater than 99 percent enantiomeric excess), chemical purity, and regulatory compliance with current Good Manufacturing Practice standards.

The hydrochloride salt is prepared by treatment of the free base with stoichiometric hydrogen chloride in an appropriate solvent (diethyl ether, isopropanol) followed by recrystallization. Product characterization includes nuclear magnetic resonance spectroscopy, mass spectrometry, chiral HPLC, and Karl Fischer titration for residual water content.

2. Abstract

Esmethadone (REL-1017) is the (S)-enantiomer of racemic methadone and a low-potency, voltage-dependent, uncompetitive antagonist of the NMDA receptor that was developed by Relmada Therapeutics as a rapid-acting antidepressant for major depressive disorder (MDD). The compound is pharmacologically distinguished from the (R)-enantiomer levomethadone by approximately 10-fold lower affinity at mu-opioid receptors (IC₅₀ approximately 26 nanomolar at mu1 versus 3 nanomolar for levomethadone) and the absence of clinically relevant opioid agonist effects, respiratory depression, reinforcing properties, and physical dependence at antidepressant doses [4, 5].

The principal pharmacological activity of esmethadone at therapeutic concentrations is uncompetitive blockade of the NMDA receptor ion channel, with IC₅₀ values of approximately 13 to 68 micromolar across GluN2A through GluN2D subunit combinations [6, 7]. Under physiological magnesium concentrations, the compound preferentially blocks tonically active GluN2D-containing receptors, a mechanism proposed to disinhibit AMPA receptor-mediated glutamatergic transmission in cortical circuits and to activate the mTORC1 signaling pathway, producing rapid antidepressant effects through BDNF-dependent synaptic plasticity [8, 9]. This mechanism is shared conceptually with ketamine and esketamine but is distinguished by the absence of dissociative and psychotomimetic effects at therapeutic doses, a property attributed to the low potency and voltage dependence of esmethadone's channel blockade, which spares phasic NMDA receptor currents required for normal neurotransmission [10].

Preclinical studies demonstrated antidepressant-like effects in multiple rodent behavioral models comparable in magnitude and duration to injectable ketamine, with the effects dependent on mTORC1 signaling in the medial prefrontal cortex and blocked by intracerebroventricular rapamycin [8]. A Phase 1 study in healthy volunteers demonstrated safety, tolerability, a pharmacokinetic profile supporting once-daily dosing (half-life exceeding 30 hours, oral bioavailability approximately 70 to 80 percent), and significant increases in circulating BDNF levels [11]. The Phase 2a randomized, double-blind, placebo-controlled trial of adjunctive esmethadone in MDD (Fava et al., 2022) demonstrated rapid improvement on the MADRS at 25 mg and 50 mg daily, with effect sizes of 0.7 to 1.0 and remission rates

of 31 to 39 percent versus 5 percent on placebo at day 14, without dissociative effects [12]. Two Phase 3 trials (Reliance I and Reliance II) were conducted; neither met its primary efficacy endpoint, and Relmada Therapeutics paused development of REL-1017 in late 2024 [13, 14]. A 12-month open-label extension study in 624 patients confirmed long-term safety, with the most common adverse events being headache, nausea, and dizziness, and no signal for abuse, dependence, or withdrawal [15].

The compound is not approved by any regulatory authority.

3. Discovery and Development History

3.1 Origin

Racemic methadone was first synthesized in 1937 by Max Bockmuhl and Gustav Ehrhart at Hoechst AG in Frankfurt, Germany, as part of an analgesic development program [1]. The compound was patented in 1941 and subsequently developed for clinical use as an analgesic and, from the 1960s onward, as an opioid substitution therapy for heroin dependence. The resolution of racemic methadone into its component (R)- and (S)-enantiomers was accomplished in the 1950s and 1960s, establishing that the (R)-enantiomer (levomethadone) carries the principal mu-opioid receptor agonist activity and that the (S)-enantiomer (esmethadone, dextromethadone) has substantially reduced opioid potency [4].

The NMDA receptor antagonist activity of methadone was first reported in the early 1990s, when electrophysiological and radioligand binding studies demonstrated that racemic methadone and both enantiomers blocked NMDA receptor currents at low micromolar concentrations [16, 17]. The recognition that the (S)-enantiomer retained the NMDA receptor antagonism while lacking the clinically relevant opioid agonism of the (R)-enantiomer created the conceptual basis for development of esmethadone as a glutamatergic neuromodulator independent of the opioid system.

3.2 Repositioning as an antidepressant

The rationale for developing esmethadone as an antidepressant emerged from two converging lines of evidence. The first was the demonstration by Zarate et al. (2006) and subsequent investigators that the NMDA receptor antagonist ketamine produces rapid antidepressant effects in treatment-resistant depression, establishing a new therapeutic paradigm for glutamatergic modulation in mood disorders [18]. The second was the growing preclinical and clinical literature on the neuroplasticity-promoting effects of NMDA receptor blockade, including the seminal Li et al. (2010) demonstration that ketamine's antidepressant activity requires mTORC1 signaling and BDNF-dependent synaptogenesis in the medial prefrontal cortex [19].

Relmada Therapeutics (New York, NY) acquired the rights to develop esmethadone as REL-1017 and initiated preclinical and clinical programs beginning approximately 2016. The company's thesis was that esmethadone, as a low-potency, voltage-dependent, uncompetitive NMDA receptor antagonist, could replicate the rapid antidepressant mechanism of ketamine without the dissociative side effects, abuse liability, and requirement for clinical supervision that limit ketamine and esketamine (Spravato) to restricted administration settings [10].

3.3 Clinical development timeline

The clinical program proceeded through the following stages:

Phase 1 (2017): Safety, tolerability, and pharmacokinetic characterization in healthy volunteers at single and multiple ascending doses (25 mg and 50 mg daily for 7 days). The study confirmed favorable safety and tolerability profiles, a long plasma half-life exceeding 30 hours, and significant increases in circulating BDNF levels [11].

Phase 2a (2019 to 2020; published 2022): A randomized, double-blind, placebo-controlled trial of adjunctive REL-1017 (25 mg and 50 mg daily for 7 days) in 62 MDD patients with inadequate response to ongoing antidepressant therapy. Principal investigator: Maurizio Fava, MD, Massachusetts General Hospital. The study demonstrated rapid and sustained antidepressant efficacy with effect sizes of 0.7 to 1.0 and remission rates of 31 to 39 percent versus 5 percent placebo [12].

Phase 3 Reliance I (2020 to 2022; published 2024): A larger randomized, double-blind, placebo-controlled trial of adjunctive REL-1017 in MDD patients with inadequate response to standard antidepressants. The trial did not meet its primary efficacy endpoint (change from baseline in MADRS-10 total score), attributed in part to a higher-than-expected placebo response during the COVID-19 pandemic enrollment period [13].

Phase 3 Reliance II (2022 to 2024): A second Phase 3 trial was initiated to confirm adjunctive efficacy. Interim analysis in late 2024 indicated that the study was unlikely to meet its primary efficacy endpoint with statistical significance. Relmada Therapeutics announced in December 2024 that the company would pause further work on REL-1017 and redirect resources to other development candidates [14].

A 12-month open-label extension study enrolled 624 MDD patients (384 rollover from double-blind studies, 202 de novo) and confirmed long-term safety and tolerability through 12 months of daily dosing [15].

An additional Phase 3 trial (NCT06735079) was registered on ClinicalTrials.gov for evaluation of REL-1017 as adjunctive treatment in MDD, with an estimated completion date of March 2027, though the status of this trial following the December 2024 pause announcement is uncertain.

3.4 Abuse potential assessment

A critical element of the development program was the formal assessment of abuse potential. A dedicated study in recreational opioid users (Relmada-sponsored, published 2023 in *Translational Psychiatry*) demonstrated that esmethadone at supratherapeutic doses produced no meaningful subjective drug effects consistent with abuse potential, no euphoria, no opioid-type effects, and no signal distinguishing it from placebo on standard abuse-potential measures [5]. This finding, combined with the absence of physical dependence and withdrawal signs in both pre-clinical (Sprague Dawley rat) and clinical studies, supported the assessment that esmethadone does not carry meaningful abuse liability [20].

4. Mechanism of Action

Esmethadone is a multi-target ligand whose principal therapeutic activity is attributed to uncompetitive NMDA receptor antagonism, with residual low-affinity opioid receptor binding that is not clinically relevant at antidepressant doses. The compound also inhibits serotonin and norepinephrine reuptake at high concentrations, though the contribution of these activities to the antidepressant mechanism at clinical doses is considered minor.

4.1 NMDA receptor antagonism

The NMDA receptor is a heterotetrameric ligand-gated cation channel composed of two obligatory GluN1 subunits and two GluN2 (GluN2A, GluN2B, GluN2C, or GluN2D) or GluN3 subunits. The receptor is activated by the simultaneous binding of glutamate and glycine (or D-serine) and requires membrane depolarization to relieve voltage-dependent magnesium block of the channel pore. NMDA receptors are expressed throughout the central nervous system and are critical for synaptic plasticity, learning, memory, and neuronal survival.

Esmethadone blocks the NMDA receptor channel pore in a voltage-dependent, uncompetitive manner, meaning that the channel must be in the open (activated) state for the drug to access the binding site within the pore [6, 7]. This kinetic property distinguishes uncompetitive antagonists from competitive antagonists (which compete with glutamate at the orthosteric site) and from negative allosteric modulators. The uncompetitive mechanism produces use-dependent blockade: receptors that are tonically overactive (as in pathological states of glutamatergic hyperactivity associated with depression, chronic stress, and neurodegeneration) are preferentially blocked, while receptors engaged in normal phasic neurotransmission are relatively spared [10].

In vitro electrophysiological studies using recombinant human NMDA receptors demonstrated IC₅₀ values for esmethadone of approximately 23 micromolar at GluN1/GluN2C, 32 micromolar at GluN1/GluN2B, 38 micromolar at GluN1/GluN2D, and 68 micromolar at GluN1/GluN2A in the absence of magnesium [6]. In the presence of physiological magnesium (1 millimolar MgCl₂), IC₅₀ values shifted to approximately 13.5 to 63.1 micromolar, with enhanced apparent selectivity for

GluN2D-containing receptors [7]. The GluN2D subtype is expressed at relatively high density on GABAergic interneurons in cortical and limbic circuits, and its tonic blockade is proposed to disinhibit pyramidal neuron glutamatergic output through AMPA receptors, a mechanism analogous to the "disinhibition hypothesis" advanced for the rapid antidepressant effects of ketamine [21].

The potency of esmethadone at the NMDA receptor is substantially lower than that of ketamine (K_i approximately 0.5 micromolar) and memantine (IC_{50} approximately 1 micromolar), placing it in the class of low-affinity channel blockers. This low potency, combined with the voltage dependence of binding, is the proposed molecular basis for the absence of dissociative and psychotomimetic effects observed in clinical studies, as phasic NMDA receptor currents associated with normal synaptic transmission are not substantially disrupted at therapeutic plasma concentrations [10].

4.2 Downstream signaling: mTORC1 and BDNF

The antidepressant mechanism of esmethadone converges on the mTORC1 signaling pathway in the medial prefrontal cortex (mPFC). Bhatt et al. (2019, published in *Neuropsychopharmacology*) demonstrated that d-methadone (esmethadone) produced rapid antidepressant-like effects in multiple rodent behavioral paradigms (forced swimming test, novelty-suppressed feeding test, female urine sniffing test) and that these effects were (a) associated with increased phosphorylation of p70S6 kinase (a downstream target of mTORC1) in the mPFC; (b) blocked by intra-mPFC infusion of the selective mTORC1 inhibitor rapamycin; and (c) associated with increased expression of synaptic proteins (PSD-95, synapsin I, GluA1) and increased dendritic spine density in layer V pyramidal neurons of the mPFC [8].

The mTORC1-dependent signaling cascade produces rapid upregulation of BDNF, which promotes dendritic spine formation, synaptic strengthening, and restoration of cortical circuit function that is impaired in major depressive disorder [19]. A Phase 1 clinical study confirmed translational relevance: healthy volunteers receiving esmethadone at 25 mg and 50 mg daily for 7 days demonstrated significant increases in circulating BDNF levels compared to placebo, providing a human biomarker bridge to the rodent mechanistic data [11].

4.3 Opioid receptor binding

Esmethadone binds to mu-opioid receptors with approximately 10-fold lower affinity than levomethadone. Kristensen et al. (1995) characterized the opioid receptor binding profiles of methadone enantiomers and reported IC₅₀ values for esmethadone of approximately 26.4 nanomolar at the mu₁ receptor and 88 nanomolar at the mu₂ receptor, compared to 3.0 nanomolar and 6.9 nanomolar, respectively, for levomethadone [4]. Affinity for delta and kappa opioid receptors was low for both enantiomers.

Despite the measurable in vitro mu-opioid binding, multiple lines of clinical and preclinical evidence demonstrate that esmethadone does not produce clinically relevant opioid agonist effects at antidepressant doses (25 to 50 mg daily): no pupil constriction, no respiratory depression, no reinforcing effects in self-administration paradigms, no physical dependence on chronic dosing, no withdrawal signs on abrupt discontinuation, and no euphoria or subjective opioid effects in a formal human abuse-potential study [5, 15, 20]. The absence of functional opioid agonism at these doses is attributed to the combination of low receptor affinity, rapid dissociation kinetics, and the predominance of NMDA receptor-mediated pharmacodynamic effects at the achieved plasma concentrations.

4.4 Serotonin and norepinephrine reuptake inhibition

Racemic methadone has been reported to inhibit serotonin and norepinephrine reuptake transporters at micromolar concentrations. The contribution of these activities to the pharmacology of esmethadone at clinical doses is considered minor relative to the NMDA receptor mechanism, though it cannot be excluded as a supplementary contributor to the antidepressant signal. The IC₅₀ values for monoamine reuptake inhibition by esmethadone are substantially higher than those for the NMDA receptor, and the clinical program did not produce evidence of serotonergic or noradrenergic adverse effects (serotonin syndrome, hypertension, tachycardia) consistent with meaningful monoamine reuptake inhibition at the studied doses.

4.5 Composite pharmacology

The composite pharmacology of esmethadone at the 25 to 50 mg oral dose range produces approximate steady-state plasma concentrations in the low micromolar range (given the long half-life and moderate volume of distribution). At these con-

centrations, NMDA receptor channel blockade is the predominant pharmacodynamic effect, with preferential tonic blockade of GluN2D-containing receptors producing downstream AMPA receptor activation, mTORC1 signaling, and BDNF-dependent synaptic plasticity. Opioid receptor occupancy is below the threshold for functional agonist effects. The net pharmacological consequence is a glutamatergic neuromodulatory profile that shares the rapid-onset antidepressant mechanism of ketamine without the dissociative liability, abuse potential, or requirement for supervised intravenous or intranasal administration.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Esmethadone is well absorbed from the gastrointestinal tract after oral administration. Oral bioavailability is approximately 70 to 80 percent, reflecting moderate first-pass hepatic metabolism [11]. Time to peak plasma concentration after oral administration of a 25 mg or 50 mg tablet is approximately 3 to 5 hours. Food effects have not been reported as clinically significant in the published pharmacokinetic studies. The favorable oral absorption supports the oral tablet formulation used in all clinical trials.

5.2 Distribution

Esmethadone has a large volume of distribution, consistent with extensive tissue partitioning and lipophilicity. Plasma protein binding is approximately 85 to 90 percent, predominantly to alpha-1-acid glycoprotein and albumin. The compound crosses the blood-brain barrier; central nervous system penetration is consistent with the observed pharmacodynamic effects on NMDA receptors in cortical and limbic structures. The high lipophilicity and large volume of distribution contribute to the long elimination half-life.

5.3 Metabolism

Esmethadone is metabolized predominantly in the liver by cytochrome P450 enzymes. The principal metabolic transformation is N-demethylation to 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), the same primary metabolite produced from racemic methadone [22]. The dominant CYP isoforms responsible for the EDDP formation are CYP3A4/5 and CYP2B6, with minor contributions from CYP2C19 and CYP2D6. EDDP is pharmacologically inactive at both NMDA and opioid receptors and is further metabolized to EMDP (2-ethyl-5-methyl-3,3-diphenylpyrroline) before excretion.

Drug-drug interaction studies demonstrated that co-administration of the strong CYP3A4 inhibitor itraconazole did not produce clinically significant changes in esmethadone pharmacokinetics, despite CYP3A4 involvement in metabolism [22]. This finding suggests that alternative metabolic pathways (principally CYP2B6) provide sufficient metabolic capacity to compensate for CYP3A4 inhibition. Esmethadone is, however, an inhibitor of CYP2D6 in vitro, and co-administration with the CYP2D6 probe substrate dextromethorphan produced a significant increase in dextromethorphan exposure, indicating a clinically relevant CYP2D6 drug interaction potential [22].

5.4 Elimination

The plasma elimination half-life of esmethadone exceeds 30 hours, supporting once-daily oral administration and achieving steady-state plasma concentrations within approximately 5 to 7 days of daily dosing [11]. Approximately half of the administered dose is recovered in urine and approximately 40 percent in feces, predominantly as the EDDP metabolite. Less than 5 percent of the dose is excreted unchanged in urine.

5.5 Special populations

A dedicated pharmacokinetic study evaluated esmethadone in subjects with chronic kidney disease and hepatic impairment [23]. In subjects with moderate hepatic impairment (Child-Pugh B), esmethadone exposure was modestly increased, consistent with the hepatic metabolism of the compound. Dose adjustment may be appropriate in moderate to severe hepatic impairment. Renal impairment did not produce clinically significant changes in esmethadone pharmacokinetics, consistent with the predominantly hepatic elimination.

5.6 Routes of administration

Esmethadone has been studied exclusively as an oral formulation in the clinical program. The compound was administered as immediate-release tablets at doses of 25 mg and 50 mg once daily. No intravenous, intramuscular, subcutaneous, or intranasal formulations have been studied or developed, consistent with the design intention of an orally bioavailable antidepressant that does not require supervised clinical administration.

6. Preclinical Pharmacology

6.1 Antidepressant-like effects in rodent behavioral models

The preclinical antidepressant characterization of esmethadone was principally conducted by the Bhatt, Bhatt, Bhatt, Bhatt and Bhatt (Bhatt et al., 2019) study and related work from the Bhatt and Bhatt laboratory. Esmethadone produced rapid antidepressant-like effects in multiple validated behavioral paradigms [8]:

Forced swimming test: Oral esmethadone reduced immobility time in mice and rats, with effect magnitude comparable to injectable ketamine (10 mg/kg intraperitoneal). The effect was observed within 24 hours of a single dose.

Novelty-suppressed feeding test: Esmethadone reduced latency to feed in a novel environment, an anxiety- and depression-sensitive paradigm. The effect was blocked by intra-mPFC rapamycin, confirming mTORC1 dependence.

Female urine sniffing test: Esmethadone increased sniffing time (a measure of hedonic motivation), with effect comparable to ketamine and blocked by rapamycin.

Chronic unpredictable stress: In a chronic stress paradigm producing sustained depressive-like behavior, esmethadone reversed sucrose preference deficits and grooming deficits, with effects sustained beyond the dosing period.

6.2 Mechanistic studies

Intracerebroventricular and intra-mPFC infusion of rapamycin (selective mTORC1 inhibitor) blocked the antidepressant-like effects of esmethadone in the forced swimming test, novelty-suppressed feeding test, and female urine sniffing test, establishing mTORC1 as a necessary downstream mediator [8]. Esmethadone increased phosphorylation of p70S6 kinase (a direct mTORC1 substrate) in the mPFC and increased expression of synaptic proteins PSD-95, synapsin I, and GluA1 (an AMPA receptor subunit), consistent with the synaptogenesis model of rapid antidepressant action [19].

6.3 Abuse and dependence liability

In Sprague Dawley rats, esmethadone did not produce conditioned place preference (a measure of reinforcing effect), did not produce physical dependence signs on chronic administration, and did not produce naloxone-precipitated withdrawal signs, confirming the absence of opioid-type dependence liability at doses producing NMDA receptor blockade [20].

6.4 Calcium influx studies

The N-Methyl-D-Aspartate Receptor Blocker REL-1017 (Esmethadone) Reduces Calcium Influx Induced by Glutamate, Quinolinic Acid, and Gentamicin, as demonstrated in cortical neuron cultures, supporting the proposed neuroprotective mechanism through reduction of excitotoxic calcium overload [6].

7. Clinical Evidence Base

7.1 Phase 1: Safety, tolerability, and pharmacokinetics in healthy volunteers

The Phase 1 study (NCT03051256) evaluated single ascending doses and multiple ascending doses (25 mg and 50 mg daily for 7 days) in healthy volunteers. The study confirmed [11]:

Safety and tolerability with no serious adverse events and no dose-limiting toxicities. Adverse events were mild and transient, principally dizziness and somnolence.

Pharmacokinetic profile supporting once-daily dosing: oral bioavailability approximately 70 to 80 percent, elimination half-life exceeding 30 hours, and linear pharmacokinetics across the studied dose range.

Significant increases in circulating BDNF levels at both 25 mg and 50 mg doses compared to placebo, providing translational biomarker evidence for the mTORC1/BDNF mechanism characterized in preclinical models.

No evidence of dissociative or psychotomimetic effects at any studied dose, as assessed by the Clinician-Administered Dissociative States Scale and the Brief Psychiatric Rating Scale.

No evidence of opioid effects, as assessed by pupillometry, the Clinical Opiate Withdrawal Scale, and subjective drug-effect questionnaires.

7.2 Phase 2a: Adjunctive treatment of MDD

The Phase 2a study (Fava et al., American Journal of Psychiatry, 2022) was a randomized, double-blind, placebo-controlled trial of REL-1017 as adjunctive treatment in 62 patients with MDD and inadequate response to 1 to 3 adequate antidepressant trials [12]. Patients were randomized 1:1:1 to placebo, REL-1017 25 mg daily, or REL-1017 50 mg daily for 7 days, with a 7-day post-treatment follow-up.

Primary efficacy endpoint: Change from baseline in MADRS-10 total score. Both REL-1017 dose groups demonstrated statistically significant improvement compared to placebo beginning at day 4 and sustained through day 7 (last dose) and day 14 (7 days after the last dose).

Effect sizes: Cohen's d effect sizes ranged from 0.7 to 1.0, indicating large effects substantially exceeding those typically observed in antidepressant clinical trials.

Remission rates (MADRS-10 less than or equal to 10) at day 14: placebo 5 percent, REL-1017 25 mg 31 percent ($p=0.035$), REL-1017 50 mg 39 percent ($p=0.01$).

Safety: Adverse events were mild to moderate and transient. No dissociative or psychotomimetic effects were observed. No opioid effects or withdrawal signs were reported. The safety profile was comparable to placebo.

A subanalysis of subjective cognitive measures from the Phase 2 trial reported improvements in cognitive symptoms in the REL-1017 treatment groups, suggesting a possible cognitive benefit secondary to the glutamatergic neuromodulatory mechanism [24].

7.3 Phase 3 Reliance I: Adjunctive treatment of MDD

The Reliance I study was a larger randomized, double-blind, placebo-controlled trial of adjunctive REL-1017 in MDD patients with inadequate response to standard antidepressants, conducted between December 2020 and December 2022 [13]. The study did not meet its primary efficacy endpoint (change from baseline in MADRS-10 total score versus placebo). The investigators and sponsor attributed the negative result in part to an elevated placebo response during the COVID-19 pandemic enrollment period, noting that placebo response rates in MDD trials conducted during this period were elevated across the field. Despite the negative primary endpoint, favorable findings on secondary measures, including response rates and clinical global impression scores, were observed, and a post hoc analysis identified a signal of efficacy in patients with antidepressant tachyphylaxis (loss of antidepressant response over time) [25].

7.4 Phase 3 Reliance II

A second Phase 3 trial (Reliance II) was initiated to confirm adjunctive efficacy. An interim analysis conducted in late 2024 indicated that the study was unlikely to meet its primary efficacy endpoint with statistical significance. In December 2024, Relmada Therapeutics announced the decision to pause further development of REL-1017 for MDD and to redirect corporate resources to other development candidates [14].

7.5 Twelve-month open-label extension

The open-label extension study enrolled 624 MDD patients (384 rollover from double-blind studies and 202 de novo participants) who received esmethadone at 25 mg or 50 mg daily for up to 12 months [15]. Key findings:

Safety: The most common treatment-related adverse events were headache (4.6 percent), nausea (4.2 percent), and dizziness (2.6 percent). No signals of meaningful neurological, cardiovascular, metabolic, or sexual adverse events were observed. No suicides or suicide attempts occurred. No cases of withdrawal syndrome were reported after discontinuation.

Efficacy: Mean change from baseline in MADRS-10 total score was approximately negative 20 to negative 22 points at 3, 6, 9, and 12 months, indicating sustained antidepressant effect in open-label treatment.

7.6 Monotherapy assessment

A Phase 3 study of esmethadone as monotherapy for MDD (NCT05081167) was registered on ClinicalTrials.gov. The current status of this trial following the December 2024 pause is uncertain. The Phase 2 data were generated exclusively in the adjunctive setting (added to ongoing, inadequately effective antidepressant therapy).

8. Sourcing and Quality Verification

Esmethadone is not commercially available as a registered pharmaceutical product in any jurisdiction. The compound is not listed in any national pharmacopoeia. Access to the compound has been exclusively through the Relmada Therapeutics clinical trial program and through research-grade chemical suppliers.

Research-grade esmethadone (as the hydrochloride salt or free base) is available from specialized chemical suppliers (Smolecule, Cayman Chemical, MedChemExpress, and others) at greater than 98 percent purity by HPLC. Supply is in milligram quantities for in vitro and in vivo research applications. Pricing is moderate to high, reflecting the limited market and the requirement for enantiomeric purity.

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 (309.21 plus or minus 0.01 for the protonated free base $[M+H]^+$, 310.22)
- Chiral HPLC or chiral gas chromatography confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (S)-enantiomer), as contamination with the (R)-enantiomer would introduce opioid agonist activity
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer titration for residual water content
- Residual solvent analysis by gas chromatography

The enantiomeric purity confirmation is especially critical for esmethadone, as even low levels of (R)-methadone contamination could confound pharmacological studies through opioid receptor activation. Third-party analytical laboratories should be engaged for independent confirmation of vendor certificates of analysis for any investigation involving in vivo administration or dose-response characterization.

Esmethadone is a derivative of methadone, which is a Schedule II controlled substance in the United States and equivalent schedules in most international jurisdictions. Investigators should confirm the regulatory scheduling status of the (S)-enantiomer in their jurisdiction before procurement, as the scheduling of individual enantiomers of controlled substances varies by jurisdiction.

9. Reconstitution and Handling

Esmethadone hydrochloride is freely soluble in water at room temperature. For in vitro research applications, the compound is typically supplied as a crystalline powder and reconstituted to stock solutions at 10 to 100 millimolar in dimethyl sulfoxide (DMSO) or at 10 to 50 mg/mL in water or normal saline for in vivo applications.

Storage: The solid compound should be stored at negative 20 degrees Celsius for long-term stability, protected from moisture and light. Room-temperature storage of the solid is acceptable for short periods (days to weeks). Aqueous stock solutions should be used within 7 to 14 days when stored at 2 to 8 degrees Celsius; DMSO stock solutions are stable for longer periods (months) at negative 20 degrees Celsius.

Aliquoting: Single-use aliquots of stock solutions are recommended to minimize freeze-thaw cycles. The compound is expected to tolerate 3 to 5 freeze-thaw cycles without significant degradation based on the chemical stability of the diphenylheptanone scaffold, but stability should be confirmed by analytical methods if freeze-thaw cycling is required.

For in vivo rodent studies, the compound has been administered orally (by gavage) in aqueous solution or suspension. The Bhatt et al. (2019) preclinical studies used oral administration, consistent with the clinical route [8].

The compound is not formulated for parenteral human administration and should not be prepared for injection in clinical-research settings without appropriate pharmaceutical development and regulatory approval.

10. Stack Interactions and Combinations

Esmethadone interacts with several drug classes through its CYP-mediated metabolism, its CYP2D6 inhibition, its NMDA receptor pharmacology, and its residual opioid receptor affinity. Investigators conducting research with esmethadone, particularly in combination with other research compounds or in participants on concurrent medications, should consider:

CYP2D6 substrates: Esmethadone is an inhibitor of CYP2D6 in vitro and produces clinically relevant increases in exposure of CYP2D6 substrates. Co-administration with dextromethorphan, codeine, tamoxifen, atomoxetine, or other CYP2D6-metabolized compounds should be approached with awareness of potential exposure increases and corresponding pharmacodynamic amplification [22].

CYP3A4 inhibitors and inducers: Despite CYP3A4 involvement in esmethadone metabolism, the strong CYP3A4 inhibitor itraconazole did not produce clinically significant pharmacokinetic changes. Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital) may reduce esmethadone exposure, though this interaction has not been formally characterized.

Other NMDA receptor antagonists: Concurrent use with ketamine, esketamine, memantine, dextromethorphan, or amantadine produces pharmacologically additive NMDA receptor blockade. The combination may increase the risk of dissociative and psychotomimetic effects and should be used only in controlled research settings.

Opioid agonists: Although esmethadone does not produce clinically relevant opioid effects at antidepressant doses, additive opioid receptor occupancy with concurrent opioid agonists (morphine, oxycodone, fentanyl, methadone, buprenorphine) cannot be excluded. Concurrent use should be monitored for opioid potentiation, though clinical evidence from the Phase 3 program did not identify this as a practical concern.

Serotonergic agents: Racemic methadone has weak serotonin reuptake inhibition. Concurrent use with serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, or other serotonergic agents should be monitored for serotonergic adverse effects, though the Phase 2 and Phase 3 programs enrolled patients on concurrent antidepressant therapy (predominantly SSRIs and SNRIs) without serotonergic adverse event signals.

QT-prolonging agents: Racemic methadone is associated with QT interval prolongation and torsade de pointes, principally attributed to hERG potassium channel blockade by the (R)-enantiomer. The contribution of esmethadone to QT prolongation risk is expected to be substantially lower than that of the racemate or levomethadone, and the clinical program did not produce a QT prolongation signal. Concurrent use with other QT-prolonging agents (fluoroquinolones, Class IA and III antiarrhythmics, certain antipsychotics) should be monitored as a precaution.

Alcohol and CNS depressants: Concurrent use with alcohol, benzodiazepines, or other central nervous system depressants should be monitored for additive sedation, though the Phase 2 and Phase 3 programs did not identify clinically significant sedative interactions.

11. Adverse Events and Safety

11.1 Common adverse events

The adverse-event profile of esmethadone across the clinical development program was favorable. In the Phase 2 and Phase 3 randomized trials, treatment-emergent adverse events were predominantly mild and transient [12, 13]:

- Headache (4 to 8 percent)
- Dizziness (3 to 5 percent)
- Nausea (3 to 5 percent)
- Somnolence (2 to 4 percent)
- Fatigue (1 to 3 percent)

These rates were comparable to or modestly higher than placebo. The 12-month open-label extension confirmed the long-term tolerability of these common adverse events, with the most frequent treatment-related adverse events being headache (4.6 percent), nausea (4.2 percent), and dizziness (2.6 percent) [15].

11.2 Absence of dissociative and psychotomimetic effects

A critical safety finding is the absence of dissociative or psychotomimetic effects at therapeutic doses (25 mg and 50 mg daily), distinguishing esmethadone from ketamine and esketamine, which produce dose-dependent dissociation, perceptual disturbances, and transient psychotomimetic symptoms that require supervised administration in clinical settings [12]. The absence of dissociative effects is attributed to the low potency and voltage-dependent, uncompetitive mechanism of esmethadone's NMDA receptor blockade, which preferentially targets tonically active receptors and spares phasic neurotransmission.

11.3 Absence of opioid effects and abuse liability

The clinical program produced no evidence of opioid agonist effects (pupil constriction, respiratory depression, euphoria, constipation consistent with mu-opioid agonism) at antidepressant doses [5, 12, 15]. The formal abuse-potential study in

recreational drug users demonstrated no meaningful abuse potential [5]. The 12-month open-label extension and the Phase 3 studies produced no evidence of physical dependence or withdrawal syndrome on discontinuation [15, 20].

11.4 Cardiac safety

Racemic methadone is associated with QT interval prolongation and torsade de pointes, principally attributed to hERG potassium channel blockade. The es-methadone clinical program monitored cardiac safety through serial electrocardiograms in Phase 1, Phase 2, and Phase 3 studies. No clinically significant QT prolongation or cardiac arrhythmia signal was identified in the published data [12, 13, 15]. The 12-month open-label extension specifically reported no signal for cardiovascular adverse events [15].

11.5 Suicidality

No suicides or suicide attempts were reported in the 12-month open-label extension study (624 patients) or in the Phase 2 and Phase 3 randomized trials [15]. Suicidal ideation was monitored using the Columbia Suicide Severity Rating Scale; no treatment-emergent suicidal ideation signal was identified.

11.6 Hepatic and renal safety

No signal for hepatic enzyme elevation or renal impairment was identified in the clinical program. The dedicated pharmacokinetic study in subjects with chronic kidney disease and hepatic impairment characterized the appropriate dose adjustment considerations for these populations [23].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five NMDA receptor-targeting or glutamatergic antidepressant candidates against esmethadone, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal glutamatergic antidepressant agents with substantive clinical evidence, with priority on compounds that share esmethadone's mechanism class or therapeutic target.

12.1 Esketamine (Spravato, Johnson and Johnson/Janssen)

Mechanism: (S)-enantiomer of ketamine; noncompetitive NMDA receptor antagonist with high potency (K_i approximately 0.5 to 1 micromolar at the NMDA receptor channel). Administered as a nasal spray under clinical supervision for treatment-resistant depression and MDD with acute suicidal ideation.

Development trajectory: FDA-approved in March 2019 as Spravato for treatment-resistant depression; expanded indication in 2020 for MDD with suicidal ideation. The most advanced and commercially successful glutamatergic antidepressant. Global sales exceeded 1 billion USD annually by 2024.

Novelty: Moderate. Esketamine is the enantiomer of a known dissociative anesthetic; the novelty lies in the repositioning for depression rather than in the molecular target.

Effect size: Large in Phase 3 registration trials. MADRS improvement versus placebo of approximately 4 to 5 points in treatment-resistant depression studies. Rapid onset (within 24 hours of first dose). Effect sustained with continued dosing.

Promising potential: High. The compound is FDA-approved and commercially established. Ongoing post-marketing studies and real-world evidence continue to support efficacy and safety.

Side-effect profile: The principal limitation is the dissociative and psychotomimetic adverse-event profile, which requires supervised administration in certified healthcare facilities for a minimum 2-hour observation period. Other adverse events include dizziness, nausea, sedation, increased blood pressure, and impaired cognition during the observation period. The REMS (Risk Evaluation and Mitigation Strategy) requirement substantially limits accessibility and convenience compared to oral antidepressants [26].

Overall validation: High. The compound has the most extensive clinical evidence base among glutamatergic antidepressants, including positive Phase 3 registration trials, FDA approval, and extensive real-world experience.

Comparison to esmethadone: Esketamine has substantially greater clinical validation and commercial success but carries the burden of dissociative side effects, supervised administration requirements, and REMS restrictions. Esmethadone's clinical thesis was predicated on replicating the rapid antidepressant mechanism without the dissociative liability, an advantage that would have been clinically significant if Phase 3 efficacy had been confirmed. The Phase 3 failure of esmethadone leaves esketamine as the only validated NMDA receptor-targeting antidepressant with regulatory approval.

12.2 Racemic ketamine (generic)

Mechanism: Noncompetitive NMDA receptor antagonist with high potency. Administered as intravenous infusion (typically 0.5 mg/kg over 40 minutes) in off-label use for treatment-resistant depression. Both enantiomers contribute to NMDA receptor blockade and to downstream mTORC1/BDNF signaling [18, 19].

Development trajectory: Not formally developed or FDA-approved for depression; widely used in off-label practice. Zarate et al. (2006) provided the landmark proof-of-concept; hundreds of clinical studies and clinical practice guidelines now support off-label intravenous ketamine for treatment-resistant depression.

Novelty: Low. Ketamine has been a clinical anesthetic since 1970; the antidepressant application is a repositioning.

Effect size: Large. Meta-analyses report MADRS or Hamilton Depression Rating Scale improvement of 10 to 15 points at 24 hours post-infusion, with Cohen's *d* effect sizes of approximately 0.8 to 1.0 versus placebo in single-infusion studies.

Promising potential: Moderate. The compound will not receive FDA approval for depression in its racemic intravenous form due to patent and commercial considerations. Its role is sustained by off-label clinical practice and by the ketamine clinic model.

Side-effect profile: Dissociation, dizziness, nausea, increased blood pressure, and transient perceptual disturbances. Requires supervised intravenous administration. Abuse potential is a concern, particularly in the outpatient clinic setting.

Overall validation: High for acute efficacy; moderate for long-term use. The evidence base is extensive but the absence of formal regulatory approval limits standardization.

Comparison to esmethadone: Racemic ketamine has a stronger acute efficacy evidence base but a less favorable side-effect profile and the requirement for intravenous administration. Esmethadone's oral bioavailability, long half-life, and absence of dissociative effects represent meaningful potential advantages, though the Phase 3 program did not confirm sufficient efficacy to capitalize on these advantages in practice.

12.3 Dextromethorphan/bupropion (Auvelity, Axsome Therapeutics)

Mechanism: Dextromethorphan is an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist; bupropion serves as a CYP2D6 metabolic inhibitor to increase dextromethorphan exposure and as an independent antidepressant (norepinephrine-dopamine reuptake inhibitor). The combination exploits the NMDA receptor antagonist mechanism of dextromethorphan while preventing its rapid CYP2D6-mediated metabolism to dextrorphan [27].

Development trajectory: FDA-approved in August 2022 as Auvelity for MDD (not restricted to treatment-resistant depression). The first oral NMDA receptor-targeting antidepressant approved by the FDA.

Novelty: Moderate to high. The fixed-dose combination of an NMDA receptor antagonist with a CYP2D6 inhibitor/antidepressant is a novel pharmacological strategy.

Effect size: Moderate. The GEMINI Phase 3 trial reported MADRS improvement of approximately 4 to 5 points versus placebo at week 6, with onset of separation from placebo at week 1.

Promising potential: High. The compound is FDA-approved and commercially available. Post-marketing experience is accumulating.

Side-effect profile: Dizziness, headache, nausea, diarrhea, somnolence. No dissociative effects at the approved dose. No supervised administration requirement. Well tolerated in the Phase 3 program.

Overall validation: High. Positive Phase 3 registration trials and FDA approval. The most direct commercial comparator to esmethadone's intended market positioning as an oral, non-dissociative, glutamatergic antidepressant.

Comparison to esmethadone: Dextromethorphan/bupropion achieved the regulatory and commercial milestone that esmethadone did not: FDA approval as an oral, non-dissociative, glutamatergic antidepressant. The mechanism is related but distinct (dextromethorphan has higher NMDA receptor affinity than esmethadone and additional sigma-1 receptor activity; the bupropion component adds norepinephrine-dopamine reuptake inhibition). The Phase 2 effect sizes for esmethadone (0.7 to 1.0) exceeded those reported for Auvelity, but this advantage was not sustained in Phase 3.

12.4 Memantine (Namenda, generic)

Mechanism: Low-affinity, voltage-dependent, uncompetitive NMDA receptor antagonist. FDA-approved for moderate to severe Alzheimer's disease dementia. The mechanism is the most directly analogous to esmethadone among approved drugs: both are low-potency, uncompetitive channel blockers that preferentially target tonically active receptors.

Development trajectory: FDA-approved in 2003 for Alzheimer's disease. Multiple clinical trials have evaluated memantine for MDD, with generally negative or inconsistent results in prospective randomized trials [28].

Novelty: Low. Memantine has been extensively studied for over two decades.

Effect size: In MDD: modest to absent. Meta-analyses of memantine as an adjunctive antidepressant have reported mixed results, with some studies showing modest benefit and others showing no significant effect. The compound has not produced consistent antidepressant signals in adequately powered prospective trials.

Promising potential: Low for depression. The compound's role in psychiatry is limited to Alzheimer's disease and off-label use in obsessive-compulsive disorder.

Side-effect profile: Favorable. Dizziness, headache, constipation, and confusion at higher doses. No dissociative effects, no abuse liability, no supervised administration requirement.

Overall validation: Low for depression; high for Alzheimer's disease.

Comparison to esmethadone: Memantine is the closest mechanistic analog to esmethadone among approved drugs, sharing the low-potency, uncompetitive, voltage-dependent NMDA receptor antagonist profile. The failure of memantine to produce consistent antidepressant signals in clinical trials raised mechanistic questions about whether low-potency NMDA channel blockade is sufficient for antidepressant activity. Esmethadone's strong Phase 2 signal and the preclinical mTORC1/BDNF evidence suggested that it might succeed where memantine had not, possibly through differences in GluN2 subtype selectivity, pharmacokinetics, or off-target activities. The Phase 3 failure of esmethadone, combined with the memantine depression data, raises the possibility that low-potency NMDA channel blockade may not be a reliable antidepressant mechanism in the general MDD population.

12.5 Rapastinel (GLYX-13, Allergan/AbbVie)

Mechanism: Functional partial agonist at the glycine site of the NMDA receptor. Unlike channel blockers (ketamine, esmethadone, memantine), rapastinel modulates NMDA receptor function through the glycine co-agonist site, producing a distinct pharmacological profile that enhances rather than blocks NMDA receptor function under certain conditions [29].

Development trajectory: Allergan advanced rapastinel through Phase 2 development for MDD with a positive Phase 2b trial (single intravenous dose produced rapid antidepressant effects at 1 and 7 days). Three Phase 3 studies were completed; all three failed to meet their primary efficacy endpoints. Development was discontinued following the negative Phase 3 readouts [29].

Novelty: High. The glycine-site partial agonist mechanism is fundamentally distinct from the channel-blocker mechanism of esmethadone, ketamine, and memantine.

Effect size: Moderate in Phase 2 (MADRS improvement of approximately 5 points versus placebo). Not significant in Phase 3.

Promising potential: Low. Development is terminated. The compound is not commercially available and is not in active development.

Side-effect profile: Favorable in Phase 2 (no dissociative effects, no psychotomimetic effects). However, the compound required intravenous administration, limiting convenience.

Overall validation: Low. The three negative Phase 3 trials are a definitive negative validation. The compound serves as a cautionary reference for the difficulty of translating Phase 2 glutamatergic antidepressant signals to Phase 3 success.

Comparison to esmethadone: Rapastinel and esmethadone share a similar clinical trajectory: positive Phase 2 signals with large effect sizes, followed by negative Phase 3 outcomes. The parallel failure of two mechanistically distinct glutamatergic antidepressant candidates in Phase 3 raises broader questions about the ability of Phase 2 MDD trial designs to predict Phase 3 outcomes and about the role of placebo response, patient selection, and trial conduct in glutamatergic antidepressant development. The two compounds are mechanistically complementary research tools: rapastinel modulates the glycine co-agonist site, while esmethadone blocks the channel pore.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the glutamatergic antidepressant pharmacology space. **Esketamine** is the only channel-blocker NMDA antagonist with FDA approval for depression, validated by positive Phase 3 trials but limited by dissociative side effects and supervised administration requirements. **Racemic ketamine** has the strongest acute efficacy evidence base in off-label practice but lacks formal regulatory approval and shares the dissociative liability. **Dextromethorphan/bupropion** achieved the commercial milestone that esmethadone did not, offering an oral, non-dissociative, glutamatergic antidepressant with FDA approval. **Memantine** is the closest mechanistic analog to esmethadone but has failed to produce consistent antidepressant signals, raising

questions about the low-potency NMDA channel-blocker mechanism. **Rapastinel** shares esmethadone's clinical trajectory of Phase 2 success followed by Phase 3 failure, highlighting the difficulty of glutamatergic antidepressant translation.

Esmethadone occupies a conceptually attractive but clinically unvalidated position in this landscape: an oral, non-dissociative, non-addictive NMDA receptor antagonist with strong Phase 2 antidepressant signals, a favorable long-term safety profile (12-month open-label data), and no abuse liability. The Phase 3 failures prevented regulatory validation of this profile. The compound remains a potentially informative research tool for understanding the pharmacology of low-potency NMDA receptor blockade, the relationship between NMDA receptor subtype selectivity and antidepressant efficacy, and the translational gap between preclinical mTORC1/BDNF signaling and clinical antidepressant outcomes.

Investigators considering esmethadone for research applications should contextualize its pharmacology within the broader glutamatergic antidepressant field: the Phase 2 efficacy signals were strong and the mechanism is well characterized, but the Phase 3 failure must temper expectations for clinical translation. The compound's principal research value lies in its unique combination of NMDA receptor antagonism without opioid agonism, dissociation, or abuse liability, properties that make it a valuable pharmacological tool for dissecting the contribution of glutamatergic mechanisms to mood regulation.

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regulatory scheduling status of the (S)-enantiomer in their jurisdiction before procurement. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Development of esmethadone (REL-1017) for major depressive disorder was paused by Relmada Therapeutics in December 2024 following negative Phase 3 interim analysis results.