

RESEARCH MONOGRAPH . COMPOUND PROFILE

Traxoprodil

A second-generation phenylethanol amine ifenprodil derivative developed at Pfizer as a forebrain-selective neuroprotectant, distinguished from first-generation NR2B antagonists by absence of alpha-1 adrenergic receptor activity and clinically evaluated in traumatic brain injury, treatment-resistant major depression, and levodopa-induced dyskinesia in Parkinson's disease.

DOCUMENT	KDC-MN-1646
ISSUED	2026-05-22
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	NR2B subunit-selective N-methyl-D-aspartate receptor antagonist

ABSTRACT

Traxoprodil (CP-101,606) is a potent and selective antagonist of N-methyl-D-aspartate (NMDA) receptors containing the NR2B (GluN2B) subunit, originally synthesized at the Central Research Division of Pfizer Inc. in Groton, Connecticut, and first disclosed by Chenard et al. in 1995 as a neuroprotectant with high selectivity for forebrain neurons. Structurally a substituted 4-phenylpiperidine and single-isomer phenylethanol amine derivative of the first-generation NR2B antagonist ifenprodil, traxoprodil retains the high-affinity NR2B binding (K_D of 4.2 nanomolar in adult rodent forebrain) while eliminating the α -1 adrenergic receptor activity that limited the clinical utility of its predecessor. The compound binds at the amino-terminal domain interface of the NR1/NR2B heterodimer and inhibits channel opening by enhancing tonic proton inhibition, a mechanism formally characterized by Mott et al. (1998) that distinguishes the phenylethanol amine class from channel-blocking NMDA antagonists such as ketamine and memantine. Pharmacokinetics in humans are dominated by hepatic cytochrome P450 2D6 (CYP2D6) metabolism, producing a striking polymorphic phenotype: in CYP2D6 extensive metabolizers, the oral bioavailability at a 100 mg dose is approximately 39.5 percent with a plasma elimination half-life of 2 to 4 hours, whereas in poor metabolizers the bioavailability approaches 80 percent with a half-life of approximately 20 hours. The nonlinear, dose-dependent oral pharmacokinetics in extensive metabolizers reflect saturation of hepatic first-pass CYP2D6 metabolism; at high oral doses the impact of CYP2D6 polymorphism on exposure diminishes as the enzyme saturates. The compound was advanced

through three principal clinical programs. In traumatic brain injury, an open-label study of 30 patients with severe head injury or spontaneous intracerebral hemorrhage demonstrated safety, tolerability, and 80 percent good recovery at 3 months; a subsequent randomized, double-blind, placebo-controlled Phase 2/3 trial of 404 severe TBI patients showed trends toward improved functional outcome (7.5 percent improvement on the dichotomized Glasgow Outcome Scale, $p = 0.07$) and reduced mortality (7 percent difference, $p = 0.08$) but did not reach conventional statistical significance. In treatment-resistant major depression, a randomized, double-blind, placebo-controlled proof-of-concept trial of 30 paroxetine-nonresponders demonstrated a 60 percent response rate on the Hamilton Depression Rating Scale after a single intravenous infusion of CP-101,606 versus 20 percent on placebo, with 78 percent of responders maintaining response for at least one week, and without dissociative side effects. In Parkinson's disease, a double-blind crossover trial in 12 patients showed approximately 30 percent reduction in levodopa-induced dyskinesia but dose-dependent dissociative and amnestic adverse events. Clinical development was ultimately discontinued due to cardiovascular safety concerns, specifically QTc interval prolongation attributed to inhibition of the human ether-a-go-go-related gene (hERG) potassium channel, a liability that Pfizer determined precluded further advancement. This monograph reviews the chemistry and stereochemistry of traxoprodil; the NR2B-selective pharmacology including the proton-enhancing mechanism and the two-class distinction among NR2B antagonists; the comprehensive CYP2D6-dependent human pharmacokinetics; the preclinical neuroprotection, antinociception, antiparkinsonian, and antidepressant pharmacology; the clinical evidence across

traumatic brain injury, treatment-resistant depression, and Parkinson's disease; and a comparative assessment of five NR2B-selective or NMDA-targeting compounds (rislenemdaz, ifenprodil, Ro 25-6981, radiprodil, and ketamine) against traxoprodil on five competency standards. The compound is not approved by any regulatory authority for any indication. It is available as a research-grade preparation; investigators should obtain analytical confirmation of identity and purity on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Traxoprodil.

Development code: CP-101,606 (Pfizer Inc.). The development code is the canonical identifier in the preclinical and clinical pharmacology literature and remains more widely cited than the nonproprietary name in primary publications through 2008 [1, 2]. The compound may also appear in older literature under the Pfizer internal project designation, though CP-101,606 is the established public-facing code.

Chemical Abstracts Service registry numbers: 134234-12-1 (free base); 189894-57-3 (mesylate hydrate salt). The mesylate salt is the formulated pharmaceutical salt used in clinical trials and in most research-grade preparations.

Unified Numbering System Identifier (UNII): UTC046R5HM.

Database identifiers: PubChem CID 219101 (free base), CID 9802399 (mesylate salt); ChEMBL ChEMBL17350. The compound is indexed in the National Center for Advancing Translational Sciences (NCATS) Inxight Drugs database and in the European Medicines Agency substance registry.

International Union of Pure and Applied Chemistry name: (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol. An alternative systematic name that appears in some databases is (S-(R*,R*))-alpha-(4-hydroxyphenyl)-beta-methyl-4-phenyl-4-hydroxy-1-piperidineethanol. The systematic name identifies the compound as a substituted 1-phenyl-2-piperidinylpropanol bearing hydroxyl groups on both the phenyl ring (para position) and the piperidine nitrogen-bearing ring (4-position) [1].

Canonical SMILES: CC@@HN1CCC(O)(c2ccccc2)CC1. The SMILES encodes both stereocenters and the connectivity of the propanol bridge linking the 4-hydroxyphenyl aromatic moiety to the 4-hydroxy-4-phenylpiperidine ring.

1.2 Structural class and chemistry

Traxoprodil belongs to the phenylethanol amine class of NR2B-selective NMDA receptor antagonists, a structural family that includes the first-generation prototype ifenprodil and the structurally related Ro 25-6981 [2, 3]. The compound is specifically a substituted 4-phenylpiperidine, bearing a 4-hydroxyphenyl group and a methyl substituent on the ethanol amine bridge that connects the piperidine ring to the aromatic pharmacophore. The 4-hydroxy group on the piperidine ring and the para-hydroxyphenyl group are both critical for NR2B binding affinity; structure-activity relationship studies at Pfizer identified these hydroxyl groups as hydrogen bond donors to residues in the NR2B amino-terminal domain [1, 7]. The methyl group on the ethanol amine bridge provides the additional steric bulk that contributes to the two-stereocentre topology and to the enhanced selectivity of the compound relative to the unsubstituted ifenprodil scaffold.

The pharmacophore common to the phenylethanol amine NR2B antagonist class consists of two aromatic rings separated by a basic nitrogen-containing linker. In traxoprodil, the piperidine ring system provides both the basic nitrogen and the second aromatic ring (as the 4-phenyl substituent), while the para-hydroxyphenyl group constitutes the first aromatic pharmacophore. The critical intramolecular distance between the two aromatic moieties and the basicity of the piperidine nitrogen are believed to determine the affinity and selectivity of the compound for the NR2B amino-terminal domain binding cleft [7].

Molecular formula: C₂₀H₂₅NO₃ (free base).

Molecular weight: 327.42 g/mol (free base). The mesylate hydrate salt (C₂₀H₂₅NO₃ plus CH₄O₃S plus H₂O) has a correspondingly higher molecular weight.

Physical properties: The free base is a white to off-white crystalline solid. The mesylate hydrate salt is the preferred form for pharmaceutical formulation owing to improved aqueous solubility and stability. The compound is soluble in dimethyl sulfoxide (DMSO) at concentrations exceeding 50 millimolar and in aqueous solutions at acidic pH; solubility in neutral aqueous media is moderate as the hydrochloride or mesylate salt. The compound is lipophilic, consistent with its ability to cross the blood-brain barrier and achieve central nervous system concentrations at therapeutically relevant plasma levels [5, 20].

Stereochemistry: Traxoprodil contains two stereocenters (at C-1 and C-2 of the propanol bridge) and is supplied as the single (1S,2S) enantiomer. The designation reflects absolute configuration determined by X-ray crystallography of the crystalline mesylate salt [1]. The compound is a single-isomer derivative of the racemic parent compound CP-98113 (Pfizer); CP-101,581 is the corresponding (1R,2R) enantiomer and has been used in stereoselectivity studies but is not the pharmacologically active form for NR2B antagonism [5]. The enantiomeric preference at the NR2B binding site is pronounced: the (1S,2S) isomer has substantially higher binding affinity than either the (1R,2R) isomer or the racemic mixture. Investigators acquiring research-grade traxoprodil should confirm enantiomeric purity by chiral high-performance liquid chromatography or by polarimetry against a reference standard, as the presence of the opposite enantiomer would alter dose-response relationships in pharmacological experiments.

1.3 Synthesis

The original synthesis of traxoprodil was disclosed by Chenard et al. in 1995 at the Pfizer Central Research Division [1]. The compound is prepared through a multi-step sequence centered on the construction of the 4-phenyl-4-hydroxypiperidine ring system, followed by stereoselective coupling with the 4-hydroxyphenyl propanol fragment. The key synthetic challenge is the installation of the (1S,2S) absolute stereochemistry with high enantiomeric excess. The 4-hydroxyphenyl group is introduced through a protected aldehyde intermediate that undergoes stereocontrolled addition to a piperidine-containing electrophile, with subsequent deprotection and resolution to yield the desired enantiomer. The final product is isolated as the free base and converted to the mesylate salt by treatment with methanesulfonic acid, followed by recrystallization from an appropriate solvent system. The compound is characterized by nuclear magnetic resonance spectroscopy (¹H and ¹³C NMR), high-resolution mass spectrometry (molecular ion at m/z 328.19 [M+H]⁺ for the free base), infrared spectroscopy, and high-performance liquid chromatography for purity assessment. Industrial preparations achieve high enantiomeric purity (greater than 99 percent enantiomeric excess) confirmed by chiral chromatography [1, 3]. The synthetic route has been adapted by multiple research chemical suppliers for small-scale production of research-grade material.

3. Discovery and Development History

3.1 Origin

Traxoprodil was synthesized at the Central Research Division of Pfizer Inc. in Groton, Connecticut, as part of a medicinal chemistry program to develop second-generation NR2B-selective NMDA receptor antagonists with improved selectivity profiles relative to ifenprodil [1]. The medicinal chemistry effort was led by Bertrand L. Chenard, with pharmacological characterization conducted by Frank S. Menniti, Keith D. Wilner, W. Frost White, Ajit K. Shah, and Stephen A. Williams at the same Pfizer division [2, 3]. The program sought to eliminate the alpha-1 adrenergic receptor activity that produced hypotension and other cardiovascular effects with ifenprodil, while retaining the high-affinity NR2B binding and forebrain-selective neuroprotection. Chenard et al. disclosed the compound in 1995, identifying it as a potent neuroprotectant that blocks NMDA responses [1]. The subsequent pharmacological characterization by Menniti et al. (1997) at Pfizer demonstrated the compound's greater than 900-fold selectivity for hippocampal neurons over cerebellar granule neurons, confirming the NR2B selectivity inferred from the structural class [2]. A comprehensive drug profile was published by Menniti et al. (1998) in *CNS Drug Reviews*, establishing CP-101,606 as the lead candidate in Pfizer's NR2B antagonist program [3]. A Morgan Stanley Dean Witter analysis in December 1998 predicted sales of \$5 million for CP-101,606 by 2001 and \$80 million by 2005, reflecting the commercial potential perceived at that time for neuroprotective agents in acute brain injury [5].

3.2 Mechanistic characterization

The molecular mechanism was elucidated by Mott et al. (1998), who demonstrated that phenylethanol amines including traxoprodil inhibit NMDA receptors by enhancing the tonic inhibition exerted by extracellular protons at physiological pH [4]. This was a significant mechanistic insight: rather than blocking the ion channel pore (as ketamine and MK-801 do) or competing at the glutamate binding site, traxoprodil enhances the sensitivity of the NR2B-containing receptor to proton inhibition, effectively shifting the pH-sensitivity curve. The NR1/NR2B receptor complex displays an IC₅₀ for proton inhibition at approximately pH 7.4, close to physiologi-

cal pH, making this receptor subtype particularly susceptible to modulators that enhance proton sensitivity [4]. Chazot et al. (2002) subsequently demonstrated that CP-101,606 defines a distinct class of NR2B antagonists: unlike Ro 25-6981, which binds with high affinity to both diheteromeric (NR1/NR2B) and triheteromeric (NR1/NR2A/NR2B) receptor complexes, CP-101,606 binds with high affinity only to diheteromeric NR1/NR2B receptors and loses affinity when an additional NR2 subunit (such as NR2A) is incorporated into the complex [6].

3.3 Clinical development

The clinical development of traxoprodil proceeded through three principal programs.

Traumatic brain injury (1997 to 2005). Pfizer advanced traxoprodil into clinical evaluation as a neuroprotectant for acute traumatic brain injury, the primary indication for which the compound was developed. Phase I trials established safety, tolerability, and pharmacokinetic parameters in healthy volunteers; by March 2000, Phase I was complete with a "good safety profile" [5]. Concurrent Phase I evaluation was initiated in Japan [5]. An open-label study in 30 patients with severe traumatic brain injury or spontaneous intracerebral hemorrhage (Bullock et al. 1999) demonstrated that 72-hour intravenous infusions at rates producing plasma concentrations exceeding 200 ng/mL were well tolerated, with 80 percent of patients achieving good recovery at 3-month follow-up [20]. A companion double-blind, placebo-controlled safety study in mild-to-moderate TBI patients (Merchant et al. 1999) confirmed the pharmacokinetic and safety parameters [21]. A pivotal randomized, double-blind, placebo-controlled Phase 2/3 trial enrolled 404 patients with severe TBI (Glasgow Coma Scale 4 to 8) and was completed in 2005 [22]. The trial showed favorable trends in the traxoprodil arm but did not achieve conventional statistical significance on the primary endpoint [22].

Treatment-resistant depression (2006 to 2008). A proof-of-concept trial of adjunctive traxoprodil for treatment-resistant major depressive disorder was conducted by Preskorn et al. (2008), producing a positive signal with 60 percent response versus 20 percent placebo [23].

Parkinson's disease dyskinesia (2006 to 2008). A double-blind crossover trial of traxoprodil as an antidyskinetic agent in levodopa-treated Parkinson's disease patients was reported by Nutt et al. (2008), showing approximately 30 percent reduction in dyskinesia severity but dose-dependent dissociative adverse events [24].

3.4 Discontinuation

Clinical development of traxoprodil was ultimately terminated due to cardiovascular safety concerns. The compound was found to inhibit the human ether-a-go-go-related gene (hERG) potassium channel, producing QTc interval prolongation on electrocardiography [30]. The hERG liability, combined with the CYP2D6 metabolic polymorphism that could elevate plasma concentrations unpredictably in poor metabolizers or in patients taking concomitant CYP2D6 inhibitors, was determined by Pfizer to preclude further clinical advancement. A 2019 review of the glutamate-based antidepressant pipeline noted that "to our knowledge, there has been no further activity in the development of this compound" [30]. Traxoprodil is not approved by the United States Food and Drug Administration, the European Medicines Agency, or any other regulatory authority for any indication. It remains available as a research-grade compound.

4. Molecular Pharmacology

Traxoprodil is a selective, high-affinity antagonist of NMDA receptors containing the NR2B (GluN2B) subunit. The compound acts at an allosteric site on the amino-terminal domain of the NR2B subunit, producing subtype-selective inhibition of receptor function through enhancement of proton-mediated tonic inhibition. The molecular pharmacology has been characterized in recombinant expression systems, primary neuronal cultures, autoradiographic binding studies, and in vivo behavioral models.

4.1 NMDA receptor background

The N-methyl-D-aspartate receptor is a heterotetrameric ligand-gated ion channel of the ionotropic glutamate receptor family, composed of two obligatory GluN1 (NR1) subunits and two GluN2 (NR2A, NR2B, NR2C, or NR2D) or GluN3 subunits [37]. The four GluN2 subtypes confer distinct biophysical, pharmacological, and expression properties on the assembled receptor. GluN2B-containing receptors are the predominant NMDA receptor population in the forebrain (hippocampus, cortex, striatum, amygdala) during development and remain highly expressed in adult hippocampus and cortex, whereas GluN2A expression increases postnatally and predominates in most brain regions by adulthood [38]. GluN2C and GluN2D are expressed principally in cerebellum and diencephalon, respectively [37, 38]. The developmental shift from NR2B to NR2A predominance is a hallmark of synapse maturation, and the NR2B subunit remains particularly enriched at extrasynaptic sites in the mature forebrain [38]. The differential regional and developmental expression of GluN2B underlies the rationale for subtype-selective antagonism: blockade of GluN2B-containing receptors can target forebrain excitotoxicity, cognition-related synaptic plasticity, and mood circuitry while sparing cerebellar and brainstem NMDA functions [2]. Channel activation requires simultaneous binding of glycine (or D-serine) to the GluN1 subunit and glutamate to the GluN2 subunit, along with membrane depolarization to relieve the voltage-dependent magnesium block of the channel pore [37].

4.2 Binding affinity and selectivity

Traxoprodil binds to NR1/NR2B receptors in HEK 293 cells with a dissociation constant (KD) of 6.0 nanomolar and to adult rodent forebrain membranes with a KD of 4.2 nanomolar, as determined by radioligand binding with tritiated CP-101,606 [6]. No high-affinity specific binding was detected to NR1 subunits expressed alone, to NR2A subunits expressed alone, to NR2B subunits expressed alone, or to NR1/NR2A diheteromeric receptors [6]. The binding site is therefore formed by the NR1/NR2B subunit interface and requires the assembled diheteromeric complex for high-affinity recognition. Importantly, Menniti et al. (1997) demonstrated that the neuroprotective activity in hippocampal neurons is mediated through a high-affinity binding site that is distinct from the agonist binding site and from the thienylcyclohexylpiperidine (TCP) channel-blocking site, establishing that the compound acts at a novel allosteric site [2].

Functionally, traxoprodil protects hippocampal neurons from glutamate-induced excitotoxicity with an IC₅₀ of approximately 11 nanomolar when applied during glutamate perfusion and approximately 35 nanomolar when applied after glutamate exposure, while being more than 900-fold less effective in protecting cerebellar granule neurons (IC₅₀ exceeding 10 micromolar) [2, 5]. This functional selectivity, approximately three orders of magnitude, reflects the predominance of NR2B-containing receptors in hippocampus and the predominance of NR2A- and NR2C-containing receptors in cerebellum. Autoradiography with radiolabeled CP-101,606 confirms that the binding site is localized to forebrain structures, most notably hippocampus and the outer layers of neocortex, with minimal binding detected in cerebellum, brainstem, or spinal cord [2].

The compound is devoid of activity at alpha-1 adrenergic receptors, the principal off-target of the first-generation NR2B antagonist ifenprodil, which produces hypotension through alpha-1 blockade [2, 3]. This selectivity improvement was a primary design objective of the Pfizer medicinal chemistry program and is the feature that distinguishes traxoprodil from its structural predecessor. Traxoprodil also lacks the sigma receptor agonism and serotonin receptor modulation that contribute to the polypharmacology of ifenprodil [3].

4.3 Mechanism of inhibition

The mechanism by which traxoprodil inhibits NR2B-containing NMDA receptors was elucidated by Mott et al. (1998), who demonstrated that phenylethanol amines enhance the tonic inhibition of NMDA receptors by extracellular protons [4]. At physiological pH (approximately 7.3 to 7.4), NMDA receptors are under partial tonic proton inhibition; the magnitude of this inhibition is subunit-dependent, with NR1/NR2B receptors showing a proton IC₅₀ near physiological pH (approximately pH 7.4), making them particularly sensitive to modulators of proton inhibition [4]. NR1/NR2A receptors, by contrast, have a proton IC₅₀ near pH 6.9, placing them further from the physiological set point and making them less sensitive to proton-enhancing modulators [4]. Traxoprodil binding at the NR2B amino-terminal domain shifts the proton inhibition curve such that a greater fraction of receptors are inhibited at any given physiological pH. The consequence is a reduction in the probability and duration of channel opening, shortening the mean open time and decreasing calcium influx through the receptor pore without directly blocking the ion channel [4, 5].

This allosteric, proton-enhancing mechanism is fundamentally distinct from the channel-blocking mechanism of ketamine and MK-801, which enter the open channel pore and physically occlude ion flow. The clinical implication is that traxoprodil does not require prior receptor activation for binding (unlike open-channel blockers) and does not produce the use-dependent blockade that can disrupt normal synaptic transmission. The mechanism also differs from competitive antagonism at the glutamate or glycine binding sites, as the compound does not compete with endogenous agonists for their recognition sites. This non-competitive, non-channel-blocking mode of action is a defining pharmacological feature of the phenylethanol amine class.

4.4 The two-class distinction among NR2B antagonists

Chazot et al. (2002) provided evidence for two distinct pharmacological classes of NR2B-selective NMDA receptor antagonists [6]. When NR1, NR2A, and NR2B subunits were co-expressed in HEK 293 cells and triheteromeric NR1/NR2A/NR2B complexes were isolated by anti-NR2A immunoaffinity chromatography, no high-affinity tritiated CP-101,606 binding sites were detected on the triheteromeric material. In contrast, parallel experiments with tritiated Ro 25-6981 demonstrated high-affinity binding to the same triheteromeric complexes [6]. This finding defines CP-

101,606 as a representative of a class of NR2B antagonists whose binding is sensitive to the subunit composition of the receptor complex: the presence of an NR2A subunit within a triheteromeric assembly disrupts the CP-101,606 binding site, likely by altering the conformation of the NR2B amino-terminal domain at the intersubunit interface. Ro 25-6981, representing the second class, binds with high affinity regardless of whether additional NR2 subunits are present [6].

The physiological significance of this distinction is considerable. Triheteromeric NR1/NR2A/NR2B receptors are abundant in the adult forebrain and constitute a substantial fraction of the total NMDA receptor population at mature synapses [38]. The CP-101,606 class of antagonists would therefore preferentially target diheteromeric NR1/NR2B receptors (enriched at extrasynaptic sites and during development), while the Ro 25-6981 class would target both diheteromeric and triheteromeric populations. This pharmacological distinction may underlie differences in the *in vivo* profiles of these two antagonist classes and has implications for the interpretation of pharmacological experiments using either compound as a "selective NR2B antagonist."

4.5 Binding site structure

Ng et al. (2008) characterized the structural determinants of the phenylethanol amine binding site in the NR2B amino-terminal domain through a combination of site-directed mutagenesis, radioligand binding, and homology modeling [7]. Three critical residues were identified: Asp101 (a charged residue), Ile150 (an aliphatic residue), and Phe176 (an aromatic residue), spatially distributed near a central cleft in the bilobed clamshell structure of the amino-terminal domain [7]. Single mutations at these positions increased the KD for Ro 25-6981 by 2.3- to 5.5-fold, while the double mutant D101A/F176A produced a 10.5-fold increase in KD [7]. Molecular modeling indicated that ifenprodil (and by extension the structurally related traxoprodil) coordinates with Asp101 through a salt bridge or hydrogen bond with the protonated piperidine nitrogen, and with Phe176 through pi-stacking or hydrophobic interactions with the aromatic pharmacophore, positioning the ligand within the putative binding cleft formed by the two lobes of the amino-terminal domain [7]. The binding affinity hierarchy among the phenylethanol amines in this study was Ro 25-6981 (KD 7 nanomolar) greater than ifenprodil (KD 60 nanomolar), consistent with the radioligand binding data for CP-101,606 (KD 4.2 to 6.0 nanomolar) placing traxoprodil at the high end of the affinity range for this structural class [6, 7].

4.6 Downstream consequences

Blockade of NR2B-containing NMDA receptors by traxoprodil reduces calcium influx through the receptor channel, with downstream consequences that include reduction of excitotoxic neuronal death (the basis of the neuroprotection application), modulation of synaptic plasticity in hippocampal and cortical circuits, and alteration of intracellular signaling cascades implicated in mood regulation. The reduction in calcium influx through extrasynaptic NR2B-containing receptors is hypothesized to attenuate pro-death signaling pathways, including those involving calpain activation and mitochondrial permeability transition, while sparing the pro-survival signaling mediated by synaptic NMDA receptors [36]. Notably, the compound has been reported to lack effects on long-term potentiation (LTP) at concentrations that produce neuroprotection, a property attributed to the preferential targeting of extrasynaptic NR2B-containing receptors over synaptic receptors involved in LTP induction [5]. This dissociation between neuroprotection and LTP disruption was a significant preclinical finding that supported advancement to clinical trials, as it suggested a therapeutic window between neuroprotective efficacy and cognitive impairment. Yang et al. (2015) demonstrated that CP-101,606 inhibits phosphorylation of the NR2B subunit at tyrosine-1472, a key post-translational modification involved in NR2B membrane trafficking and synaptic anchoring, and disrupts the interaction between NR2B and the Src family kinase Fyn in striatal tissue of rats with levodopa-induced dyskinesia [19]. This molecular mechanism provides a basis for the antidyskinetic effects observed in preclinical and clinical Parkinson's disease studies.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and bioavailability

The oral pharmacokinetics of traxoprodil were comprehensively characterized by Taylor et al. (2006) in a three-way crossover study of healthy male volunteers phenotyped as CYP2D6 extensive metabolizers (n = 11) or poor metabolizers (n = 6) [8]. Traxoprodil was administered as single oral doses of 50, 100, and 300 mg and as intravenous infusions of 50 and 100 mg over 2 hours. The study design permitted direct calculation of absolute oral bioavailability by comparing oral and intravenous AUC values within each metabolizer group.

In CYP2D6 poor metabolizers, oral bioavailability was approximately 80 percent, consistent with a liver extraction ratio of approximately 20 percent and near-complete gastrointestinal absorption [8]. The bioavailability was linear and dose-independent across the studied dose range, and maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased approximately proportionally with dose [8]. The near-complete oral absorption in poor metabolizers indicates that the gastrointestinal tract does not limit systemic availability and that the low bioavailability observed in extensive metabolizers is attributable entirely to hepatic first-pass metabolism [8].

In CYP2D6 extensive metabolizers, oral bioavailability was nonlinear and dose-dependent. At the 100 mg dose, absolute oral bioavailability was approximately 39.5 percent; across all doses, bioavailability ranged from 22.8 to 62.1 percent [8]. C_{max} and AUC increased more than proportionally with dose, and apparent oral clearance decreased with increasing dose, consistent with saturation of hepatic first-pass CYP2D6 metabolism [8]. At the highest oral dose of 300 mg, maximum plasma concentrations of approximately 674 ng/mL were achieved. Time to maximum concentration (T_{max}) was generally 1 to 3 hours after oral dosing in both metabolizer groups [8].

5.2 Distribution

Following intravenous administration in CYP2D6 poor metabolizers, the mean volume of distribution at steady state (V_{ss}) was approximately 6.5 L/kg, indicating extensive tissue partitioning well beyond total body water [8]. In extensive metabolizers, V_{ss} was approximately 4 L/kg, still indicative of substantial tissue distribution [8]. The large V_{ss} is consistent with the lipophilic character of the compound and its ability to cross the blood-brain barrier. The Bullock et al. (1999) open-label study reported that intravenous infusion achieved cerebrospinal fluid penetration at therapeutic plasma concentrations, consistent with the forebrain-localized autoradiographic binding signal [2, 20]. Intravenous infusion rates used in clinical trials achieved plasma concentrations of 100 to 200 ng/mL in the traumatic brain injury studies [20, 21], with the Nutt et al. (2008) Parkinson's disease study reporting achieved maintenance plasma concentrations of 109 ng/mL at the low dose and 294 ng/mL at the high dose [24]. Protein binding data for traxoprodil in humans have not been published in the peer-reviewed literature; investigators should consider this gap when interpreting the relationship between total plasma concentrations and pharmacological effect.

5.3 Metabolism

Traxoprodil is metabolized predominantly by CYP2D6 in the liver [8]. The CYP2D6 dependence is the source of the polymorphic pharmacokinetic phenotype that is the single most important pharmacokinetic feature of the compound. CYP2D6 poor metabolizers (approximately 5 to 10 percent of European-ancestry populations, approximately 1 to 2 percent of East Asian populations) exhibit dramatically different pharmacokinetic parameters from extensive metabolizers owing to the absence of functional CYP2D6 enzyme activity. In poor metabolizers, the plasma elimination half-life is approximately 20 hours and plasma clearance following intravenous administration is approximately 4 mL/min/kg [8]. In extensive metabolizers, the plasma elimination half-life is approximately 2 to 4 hours (consistent across oral doses of 50, 100, and 300 mg) and plasma clearance is approximately 27 mL/min/kg, nearly seven-fold higher than in poor metabolizers [8]. The oral elimination half-life in extensive metabolizers did not change substantially across the dose range studied, even though oral bioavailability increased with dose, suggesting that the saturation of CYP2D6 affects primarily the first-pass extraction rather than systemic clearance at the doses tested [8].

The saturable nature of CYP2D6-mediated first-pass metabolism means that at high oral doses, the pharmacokinetic difference between extensive and poor metabolizers narrows, as the enzyme becomes saturated in extensive metabolizers and the impact of CYP2D6 polymorphism on systemic exposure diminishes [8]. This convergence at high doses has implications for dose selection in any future clinical investigation: high oral doses would partially mitigate the variability introduced by CYP2D6 polymorphism, but at the cost of higher plasma concentrations and a narrower therapeutic index.

5.4 Effects on hepatic CYP enzymes

Bromek et al. (2021) characterized the effects of repeated CP-101,606 administration (20 mg/kg intraperitoneally for 5 days or 3 weeks) on hepatic cytochrome P450 enzyme expression in rats [9]. After 5 days of treatment, significant suppression of multiple CYP isoforms was observed: CYP1A activity was reduced by 68.6 percent, CYP2A by 68.7 percent, CYP2B by 74.8 percent, CYP2C11 by 60.9 to 76.7 percent, and CYP3A by 77 to 79.8 percent [9]. After 3 weeks of treatment, most acute effects had diminished, though CYP3A protein suppression persisted [9]. The authors proposed that the CYP modulation occurs via suppression of the hypothalamic-pituitary-adrenal axis (reduced growth hormone-releasing hormone and serum growth hormone) rather than through direct hepatic enzyme inhibition, representing a novel neuroendocrine mechanism of drug-metabolism modulation by glutamatergic compounds [9]. The clinical translatability of these findings to humans at therapeutic doses is unknown.

5.5 Routes of administration

The principal route of administration in clinical trials has been intravenous infusion, reflecting the neuroprotection indication that required rapid achievement of therapeutic plasma concentrations in acute brain injury. Infusion protocols used in published studies include: initial loading at 0.75 mg/kg/hr for 2 hours followed by maintenance at 0.37 mg/kg/hr for up to 72 hours (traumatic brain injury studies) [20]; and lower-dose protocols of 0.25 mg/kg/hr loading for 2 hours followed by 0.12 mg/kg/hr maintenance (Parkinson's disease study low-dose arm) [24]. Oral administration was studied in the pharmacokinetic characterization at doses of 50 to 300 mg [8] but has not been the primary route in published efficacy trials. The oral route presents challenges for the neuroprotection indication (delayed onset, vari-

able bioavailability in CYP2D6 extensive metabolizers) but would be the preferred route for chronic indications such as depression, where rapid onset is less critical and steady-state plasma concentrations can be achieved over days.

5.6 Special populations

Formal special-population pharmacokinetic studies in renal impairment, hepatic impairment, geriatric subjects, and pediatric subjects have not been published in the peer-reviewed literature. Given the dominant CYP2D6-mediated hepatic metabolism, hepatic impairment would be expected to reduce first-pass extraction and increase systemic exposure, particularly in CYP2D6 extensive metabolizers. Renal impairment effects have not been characterized; the large V_{ss} and hepatic clearance pathway suggest that renal elimination of unchanged drug is not a major route, but metabolite accumulation in renal impairment cannot be excluded without formal study. The CYP2D6 polymorphism is the dominant source of interindividual pharmacokinetic variability and should be considered a critical covariate in any research protocol. Investigators conducting studies with traxoprodil should consider CYP2D6 genotype or phenotype assessment for dose-response interpretation, particularly when using oral dosing.

6. Preclinical Pharmacology

6.1 Neuroprotection

The primary preclinical application for which traxoprodil was developed is neuroprotection against glutamate-mediated excitotoxicity. Menniti et al. (1997) demonstrated that CP-101,606 potently and efficaciously protected hippocampal neurons from glutamate toxicity in primary culture, with an IC₅₀ of approximately 11 nanomolar when applied during glutamate perfusion and approximately 35 nanomolar when applied after glutamate exposure [2]. The compound was more than 900-fold less effective in protecting cerebellar granule neurons, with no significant neuroprotection observed at concentrations up to 10 micromolar [2]. This selectivity ratio is among the largest reported for any neuroprotective agent across neuronal populations and reflects the differential expression of NR2B-containing receptors in forebrain versus cerebellum. Autoradiographic studies confirmed that the CP-101,606 binding site is localized to forebrain structures, most notably hippocampus and the outer layers of neocortex, consistent with the known distribution of NR2B-containing NMDA receptors [2]. The neuroprotective mechanism was mediated through a high-affinity binding site distinct from the agonist binding site and from the TCP channel-blocking site, as demonstrated by the failure of TCP-site ligands to displace CP-101,606 binding [2].

The neuroprotective activity extended to a developmental model. Bhagwandin et al. (2020) examined CP-101,606 in a rat model of third-trimester-equivalent ethanol exposure, using both organotypic hippocampal slice cultures and in vivo neonatal ethanol intubation [17]. In hippocampal slices exposed to chronic ethanol (100 millimolar for 10 days), CP-101,606 at concentrations of 10 and 25 nanomolar significantly reduced cell death in the CA1 pyramidal layer [17]. In the in vivo model, a single subcutaneous injection of 15 mg/kg administered approximately 21 hours after the final ethanol exposure attenuated both cellular damage and behavioral deficits including hyperactivity, impaired balance, and spatial memory deficits [17]. The specificity of CP-101,606 for NR2B-containing diheteromeric receptors was noted by the authors as a distinguishing feature relative to other NR2B antagonists that also block triheteromeric receptors [17].

6.2 Antinociception

Taniguchi et al. (1997) characterized the analgesic activity of CP-101,606 in three rat pain models: carrageenan-induced mechanical hyperalgesia, capsaicin-induced nociception, and 4-beta-phorbol-12-myristate-13-acetate (PMA)-induced nociception [10]. CP-101,606 at 30 mg/kg subcutaneously suppressed mechanical hyperalgesia at 0.5 and 2.5 hours after carrageenan challenge [10]. In the capsaicin and PMA nociceptive tests, the ED₅₀ values were 7.5 and 5.7 mg/kg subcutaneously, respectively [10]. Importantly, the analgesic effects were observed "without any apparent alterations in motor coordination or behaviour," distinguishing the compound from broad-spectrum NMDA antagonists that produce motor impairment at analgesic doses [10].

Nakazato et al. (2005) extended the analgesic characterization to a chronic constriction injury (CCI) model of neuropathic pain and demonstrated a critical anatomical dissociation [11]. Subcutaneous CP-101,606 at 10 mg/kg significantly inhibited CCI-induced mechanical allodynia, and intracerebroventricular injection at 100 nanomoles also inhibited allodynia in a dose-dependent manner [11]. However, intrathecal injection of CP-101,606 at 300 nanomoles failed to inhibit allodynia, while the non-selective NMDA antagonist memantine at the same intrathecal dose was effective [11]. The authors concluded that "the anti-allodynia effect of CP-101,606 is ascribable to blockade of NR2B receptors at the brain, but not at the spinal cord," consistent with the forebrain localization of NR2B-containing receptors identified by autoradiography and with the low density of NR2B subunit expression in adult spinal cord [11].

6.3 Antiparkinsonian activity

Steece-Collier et al. (2000) evaluated the antiparkinsonian potential of CP-101,606 in both rodent and primate models [12]. In rats, CP-101,606 decreased haloperidol-induced catalepsy with an ED₅₀ of approximately 0.5 mg/kg, indicating direct antiparkinsonian activity at low doses [12]. In MPTP-treated rhesus monkeys, CP-101,606 at 1 mg/kg reduced parkinsonian motor symptoms by 20 percent as monotherapy [12]. At a lower dose of 0.05 mg/kg in combination with a submaximal dose of levodopa, CP-101,606 reduced motor symptoms by approximately 50 percent compared to vehicle and approximately 30 percent compared to levodopa alone, demonstrating synergistic potentiation of the antiparkinsonian effect [12]. No side effects were apparent at any dose tested in either species [12].

However, results in the MPTP-lesioned marmoset model were more complex and contradictory. Nash et al. (2004) reported that CP-101,606 at doses of 1 and 3 mg/kg exacerbated levodopa-induced dyskinesia while providing mild potentiation of the antiparkinsonian effects of levodopa [13]. The discrepancy between the rhesus and marmoset findings may reflect species differences in NR2B receptor distribution within basal ganglia circuits, differences in the severity and chronicity of the MPTP lesion model, or differences in the dyskinesia assessment methodology. This species discrepancy illustrates the challenges of translating NR2B antagonist pharmacology across preclinical models and should be considered when interpreting the human Parkinson's disease data.

6.4 Antidepressant activity

Poleszak et al. (2016) characterized the antidepressant-like activity of traxoprodil in the mouse forced swim test [14]. Traxoprodil administered intraperitoneally at doses of 20 and 40 mg/kg significantly reduced the total duration of immobility, a behavioral index of antidepressant-like activity [14]. At a subtherapeutic dose of 10 mg/kg, traxoprodil potentiated the antidepressant-like effects of imipramine (15 mg/kg), fluoxetine (5 mg/kg), and escitalopram (2 mg/kg), but not of the selective noradrenaline reuptake inhibitor reboxetine (2.5 mg/kg) [14]. The selectivity of the potentiation for serotonergic and mixed-mechanism antidepressants but not for the pure noradrenergic reuptake inhibitor suggests a serotonin-mediated component of the interaction. Depletion of serotonin with para-chlorophenylalanine (p-CPA) partially reversed the antidepressant-like effect of traxoprodil, providing pharmacological confirmation of partial serotonin dependence of the antidepressant mechanism [14]. Notably, co-administration of traxoprodil significantly increased brain concentrations of imipramine, desipramine, and escitalopram, suggesting a pharmacokinetic interaction at the metabolic level (likely CYP inhibition) that may contribute to the observed potentiation in addition to any pharmacodynamic synergy [14]. The antidepressant-like effects were not related to changes in locomotor activity, ruling out motor confounds [14].

Popik et al. (2016) further demonstrated that traxoprodil augmented the antidepressant-like activity of agomelatine (a melatonin MT₁/MT₂ agonist and 5-HT_{2C} antagonist) but not of mianserin or tianeptine in the forced swim test, suggesting selectivity in the antidepressant combinations that benefit from NR2B antagonist augmentation [15].

6.5 Abuse potential and discriminative stimulus

Nicholson et al. (2007) evaluated the phencyclidine (PCP)-like properties of CP-101,606 in drug discrimination and self-administration paradigms [16]. In rats trained to discriminate PCP from saline, CP-101,606 produced greater than 80 percent PCP-lever selection at 2.0 mg/kg intraperitoneally [16]. In rhesus monkeys, CP-101,606 produced greater than 90 percent PCP-lever selection at 0.1 mg/kg intramuscularly [16]. Self-administration studies in rhesus monkeys demonstrated reinforcing effects in all four animals tested [16]. However, unlike PCP itself, response rates remained largely unaffected at doses producing full substitution in monkeys, suggesting a potentially improved behavioral profile despite the PCP-like discriminative stimulus [16]. These findings indicate that NR2B-selective antagonism does not fully eliminate the PCP-like subjective effects of NMDA receptor blockade, a consideration relevant to the abuse potential assessment of this compound class.

6.6 Cognitive effects

The effect of CP-101,606 on cognitive function in preclinical models has yielded complex results. The compound was reported to lack effects on long-term potentiation (LTP) at neuroprotective concentrations, and to lack the amnesic side effects of other NMDA receptor antagonists at these concentrations [5]. This dissociation between neuroprotection and cognitive impairment was attributed to the preferential targeting of extrasynaptic NR2B-containing diheteromeric receptors, which are less involved in LTP induction than synaptic NMDA receptors [5, 6]. In the Morris water maze, racemic CP-101,606 was evaluated for effects on spatial learning and hippocampal plasticity, with results suggesting that the compound does not impair spatial learning at doses relevant to neuroprotection [18]. Yang et al. (2015) demonstrated that CP-101,606 inhibits NR2B phosphorylation at tyrosine-1472 and disrupts NR2B interactions with the Fyn kinase in a rat model of levodopa-induced dyskinesia, providing a molecular mechanism for the observed effects on striatal synaptic plasticity that is distinct from the acute neuroprotective mechanism [19].

7. Clinical Evidence Base

The clinical evidence base for traxoprodil comprises three principal programs: traumatic brain injury (the primary development indication), treatment-resistant major depression, and Parkinson's disease dyskinesia. The compound is not approved for any indication by any regulatory authority. The following data are presented for the use of the research community and do not constitute therapeutic recommendations.

7.1 Traumatic brain injury: open-label study

Bullock et al. (1999) reported an open-label study of CP-101,606 in 30 patients with acute severe traumatic brain injury (Glasgow Coma Scale 3 to 8) or spontaneous intracerebral hemorrhage, conducted at a single center [20]. Twenty patients had traumatic brain injury and 10 had spontaneous intracerebral hemorrhage. The compound was administered as intravenous infusion at an initial rate of 0.75 mg/kg/hr for 2 hours followed by 0.37 mg/kg/hr continuation, with infusion durations of 2 hours (n = 17), 24 hours (n = 2), or 72 hours (n = 11) [20]. The escalating infusion-duration design permitted initial safety evaluation at shorter exposures before advancing to the 72-hour infusion protocol planned for the Phase 2/3 trial. Plasma concentrations exceeding 200 ng/mL were achieved within 2 hours of infusion initiation [20]. No adverse events were considered drug-related, and no clinically significant hematological abnormalities or electrocardiographic changes were observed during the study period [20]. At 3-month follow-up, 80 percent of patients had good recovery, and patients receiving extended infusions (24 or 72 hours) showed improved outcomes compared to the 2-hour protocol group, though the open-label design and small sample preclude causal inference [20].

Merchant et al. (1999) reported a companion double-blind, placebo-controlled study of the safety, tolerability, and pharmacokinetics of CP-101,606 in patients with mild or moderate traumatic brain injury (Glasgow Coma Scale 9 to 15), confirming the pharmacokinetic and safety parameters observed in the open-label study and providing the controlled safety data that supported advancement to the pivotal Phase 2/3 trial [21].

7.2 Traumatic brain injury: Phase 2/3 trial

Yurkewicz et al. (2005) reported the pivotal randomized, double-blind, placebo-controlled study assessing the efficacy and safety of a 72-hour infusion of traxoprodil compared to placebo in 404 patients with severe TBI (GCS 4 to 8), treated within 8 hours of injury [22]. Subjects were stratified by motor score severity at baseline to ensure balanced randomization across injury severity. The infusion protocol paralleled that of the Bullock open-label study: loading at 0.75 mg/kg/hr followed by maintenance infusion for 70 additional hours [22]. On the primary endpoint (dichotomized Glasgow Outcome Scale at 6 months), a greater proportion of traxoprodil-treated subjects had favorable outcomes (delta 5.5 percent, odds ratio 1.3, $p = 0.21$, 95% CI 0.85 to 2.06) [22]. At last visit, the difference was larger (delta 7.5 percent, odds ratio 1.47, $p = 0.07$, 95% CI 0.97 to 2.25) [22]. Mortality with traxoprodil was 7 percent lower than with placebo (odds ratio 1.45, $p = 0.08$, 95% CI 0.96 to 2.18) [22]. In the most severe subset of patients (lowest motor score stratum), treatment differences were more pronounced: 11.8 percent improvement on the dichotomized Glasgow Outcome Scale at last visit and 16.6 percent mortality reduction [22].

The authors concluded that "no definitive claim of efficacy can be made for traxoprodil for the treatment of severe TBI," despite the consistent trend toward benefit across all endpoints and the more pronounced effects in the most severely injured patients [22]. Traxoprodil was well tolerated in this critically ill population, with no treatment-emergent safety signals specific to the active treatment group [22]. The trial results are representative of a broader pattern in TBI neuroprotection research, in which agents showing strong preclinical efficacy have failed to achieve conventional statistical significance in large Phase 2/3 studies, a challenge attributed to heterogeneity of the TBI population, the coarseness of the Glasgow Outcome Scale as an endpoint instrument, and the difficulty of achieving adequate target exposure in the acute injury setting [35].

7.3 Treatment-resistant depression

Preskorn et al. (2008) reported a randomized, placebo-controlled, double-blind proof-of-concept study evaluating the antidepressant efficacy of CP-101,606 in patients with treatment-refractory major depressive disorder [23]. The study employed a sequential enrichment design: in Period 1, subjects received 6 weeks of open-label paroxetine plus a single-blind intravenous placebo infusion; Period 1

nonresponders (n = 30) were then randomized to receive a single double-blind infusion of CP-101,606 or placebo plus continued paroxetine for up to 4 additional weeks (Period 2) [23]. This enrichment design ensured that the study population had demonstrated treatment resistance to an adequate trial of a selective serotonin reuptake inhibitor before being randomized to the experimental arm.

On the prespecified primary outcome measure (change from baseline in the Montgomery-Asberg Depression Rating Scale total score at day 5 of Period 2), CP-101,606 produced a greater decrease than placebo, with a mean difference of 8.6 points (80% confidence interval, negative 12.3 to negative 4.5; p less than 0.10) [23]. The 80% confidence interval was used rather than the conventional 95% interval because the study was explicitly designed as a proof-of-concept trial powered to detect large effects rather than to provide confirmatory evidence [23]. The Hamilton Depression Rating Scale response rate (50 percent or greater reduction from baseline) was 60 percent for CP-101,606 versus 20 percent for placebo [23]. Seventy-eight percent of CP-101,606 responders maintained response status for at least 1 week after the infusion, with a median duration of response of approximately 2 weeks, indicating that the antidepressant effect outlasted the pharmacokinetic presence of the compound [23].

Critically, CP-101,606 was "safe, generally well tolerated, and capable of producing an antidepressant response without also producing a dissociative reaction" [23]. This absence of dissociative effects distinguished traxoprodil from ketamine, which produces robust dissociative and psychotomimetic effects at antidepressant doses, and was considered a significant advantage for the NR2B-selective approach to glutamatergic antidepressant development. The result was interpreted by the field as evidence that NR2B-selective antagonism may capture a meaningful component of the rapid antidepressant mechanism of NMDA receptor modulation with a more favorable subjective-effect profile than non-selective blockade [30, 33].

7.4 Parkinson's disease dyskinesia

Nutt et al. (2008) reported a randomized, double-blind, placebo-controlled crossover trial examining the acute effects of CP-101,606 on levodopa-induced dyskinesia and parkinsonism in 12 Parkinson's disease patients with motor fluctuations [24]. Subjects received 4-hour intravenous infusions on three separate days: low-dose CP-101,606 (0.25 mg/kg/hr for 2 hours, then 0.12 mg/kg/hr), high-dose CP-101,606

(0.75 mg/kg/hr for 2 hours, then 0.36 mg/kg/hr), or placebo [24]. During hours 1 to 3, all subjects received concomitant levodopa infusion to induce dyskinesia under controlled conditions [24].

Both doses of CP-101,606 reduced the maximum severity of levodopa-induced dyskinesia by approximately 30 percent compared to placebo, with similar effect sizes at low and high doses (low dose: negative 1.83 least squares mean difference versus placebo, 95% CI negative 2.62 to negative 1.05; high dose: negative 1.79, 95% CI negative 2.57 to negative 1.01) [24]. The antidyskinetic effect was not dose-dependent, suggesting a ceiling effect within the studied concentration range [24].

However, CP-101,606 was associated with dose-dependent dissociative and amnesic adverse events: some combination of abnormal thinking, depersonalization, and amnesia occurred in 10 of 12 subjects receiving the high dose and 5 of 12 subjects receiving the low dose [24]. Finger tapping speed, an index of motor function, was reduced in a dose-dependent manner with CP-101,606, though motor UPDRS scores at peak levodopa response showed similar improvement across all treatments, suggesting that the tapping reduction "might not be due to antagonism of the antiparkinsonian actions of levodopa but to the mental effects" [24]. Plasma concentrations achieved during maintenance were 109 ng/mL at the low dose and 294 ng/mL at the high dose [24]. No significant effects on blood pressure, heart rate, or QT interval were detected in this small study [24]. CP-101,606 did not alter levodopa pharmacokinetics [24].

7.5 Development status and ongoing trials

There are no known active clinical trials of traxoprodil as of the date of this monograph. Clinical development was terminated by Pfizer due to QTc prolongation concerns [30]. No subsequent sponsor has disclosed active development of the compound. The compound remains available as a research tool for preclinical and translational studies of NR2B-selective NMDA receptor antagonism.

8. Sourcing and Quality Verification

Traxoprodil is not a registered pharmaceutical product in any jurisdiction. Research-grade material is the only available source for laboratory and investigational use. The compound is not approved for human therapeutic use, and material obtained through research chemical suppliers is designated for research use only.

The compound is supplied by multiple research chemical vendors, including MedChemExpress, BenchChem, MedKoo Biosciences, Tocris, Sigma-Aldrich (MilliporeSigma), and Cayman Chemical, typically as the mesylate hydrate salt at purities of 98 percent or greater by high-performance liquid chromatography (HPLC). Supply is available in milligram to gram quantities. The free base is also available from some suppliers, though the mesylate salt is the preferred form for most research applications owing to improved aqueous solubility, crystalline stability, and consistency with the clinical formulation. Pricing and availability should be confirmed with individual vendors, as research-grade supply of discontinued clinical candidates can be intermittent.

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

- Reversed-phase HPLC area-percent purity assessment, with a target of greater than 98 percent purity, and comparison to a reference standard where available
- Mass spectrometry confirmation of molecular weight: expected $[M+H]^+$ at m/z 328.19 for the free base ($C_{20}H_{25}NO_3$), or m/z 424.18 for the mesylate salt $[M+H]^+$ accounting for the methanesulfonate counterion
- Chiral HPLC confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (1S,2S) form), as the (1R,2R) enantiomer (CP-101,581) has distinct pharmacological properties and its presence as an impurity would confound dose-response relationships in NR2B binding and neuroprotection assays [5]
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, with comparison to published spectral data
- Karl Fischer titration or loss-on-drying analysis for residual water content, particularly for the hydrate salt form, as variable hydration states can affect

gravimetric dose accuracy

- Residual solvent analysis by gas chromatography for common synthesis solvents (dimethylformamide, dichloromethane, methanol, ethyl acetate)

Common impurities to monitor include the (1R,2R) enantiomer, the racemic parent compound CP-98113, incompletely resolved diastereomers, and dehydration products of the piperidine hydroxyl group. Third-party analytical laboratories provide independent verification of vendor certificates of analysis. Because traxoprodil is not a registered medicine and the research-grade market is relatively small, lot-to-lot variability may be observed; on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is critical.

The compound is classified as a research chemical and is not subject to controlled substance scheduling in the United States or European Union. Import and export regulations for research chemicals apply. Investigators should maintain documentation of sourcing, purity verification, and intended research use in compliance with institutional review requirements.

9. Reconstitution and Handling

9.1 In vitro preparations

Traxoprodil mesylate hydrate is moderately soluble in aqueous solutions. For in vitro research applications, the compound is typically prepared as a concentrated stock solution in dimethyl sulfoxide (DMSO) at 10 to 50 millimolar, then diluted into aqueous assay buffer immediately before use. The final DMSO concentration in the assay should be maintained below 0.1 percent (v/v) to avoid solvent effects on NMDA receptor function, as DMSO at higher concentrations can modulate ion channel activity. Stock solutions should be prepared gravimetrically using analytically verified compound mass and molecular weight corrections for the salt form and hydration state.

9.2 In vivo preclinical preparations

For in vivo preclinical studies, the compound has been administered by intraperitoneal injection (dissolved in saline or saline with a small percentage of DMSO or polyoxyethylene sorbitan monooleate [Tween-80] as needed to achieve solution clarity), by subcutaneous injection, and by intravenous infusion. Published preclinical doses range from 0.05 mg/kg (in combination studies with levodopa [12]) to 40 mg/kg (in forced swim test antidepressant studies [14]), with the dose, route, vehicle composition, and injection volume specified in each study protocol. For subcutaneous and intraperitoneal routes, the compound may be dissolved in 0.9 percent saline at acidic pH (pH 4 to 5, adjusted with dilute hydrochloric acid) to take advantage of the improved solubility of the protonated amine form; the solution should be brought to neutral pH before injection if the acidic vehicle would cause injection-site irritation at the volume administered.

9.3 Clinical formulations

For clinical-research formulations, the compound was supplied as a sterile aqueous solution for intravenous infusion in the Pfizer-sponsored trials. The specific clinical formulation details (buffer composition, pH, concentration, excipients) have not been published in the peer-reviewed literature in detail; investigators requiring

parenteral preparations for research use should consult pharmaceutical compounding resources and validate sterility, pyrogenicity, stability, and compatibility with intravenous administration sets under their specific conditions.

9.4 Storage and stability

Storage of the solid compound is recommended at negative 20 degrees Celsius for long-term storage (greater than 6 months) and at 2 to 8 degrees Celsius for working stocks that will be consumed within weeks. The compound should be protected from light and moisture; the mesylate hydrate salt should be stored in desiccated conditions to prevent variable hydration that could affect gravimetric accuracy. DMSO stock solutions should be aliquoted into single-use volumes to avoid repeated freeze-thaw cycles, which may cause precipitation or degradation; stability data for frozen DMSO stocks have not been formally published for this compound, and investigators should validate potency retention under their specific storage conditions by periodic HPLC re-analysis. Aqueous solutions should be prepared fresh or used within 24 hours of preparation unless stability has been independently validated, as the compound may undergo hydrolysis or oxidation in aqueous media over extended periods, particularly at neutral or alkaline pH.

10. Stack Interactions and Combinations

Traxoprodil interacts with several drug classes through its CYP2D6-dependent metabolism, its broad suppression of hepatic CYP enzymes observed in preclinical studies, its NMDA receptor pharmacology, and its hERG channel activity. Investigators conducting research with traxoprodil should consider the following interaction categories.

CYP2D6 inhibitors and substrates. Traxoprodil is a CYP2D6 substrate and may also inhibit CYP2D6 activity. Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine, terbinafine) would be expected to increase traxoprodil exposure, particularly in CYP2D6 extensive metabolizers where first-pass metabolism is the primary determinant of bioavailability. The Preskorn et al. (2008) trial was designed with paroxetine (a strong CYP2D6 inhibitor) as the background antidepressant, creating a pharmacokinetic interaction that would have elevated traxoprodil exposure in extensive metabolizers toward the poor-metabolizer phenotype [23]. This interaction was by design in the Preskorn trial (to reduce pharmacokinetic variability across CYP2D6 genotypes), but investigators should consider it when interpreting the Preskorn trial results and when designing research protocols with concomitant CYP2D6-interacting agents. Conversely, CYP2D6 inducers (if any; CYP2D6 is generally considered non-inducible, though some evidence suggests minor induction) would not be expected to substantially alter traxoprodil exposure.

Hepatic CYP enzyme substrates. The Bromek et al. (2021) finding that repeated CP-101,606 administration in rats suppresses CYP1A, CYP2A, CYP2B, CYP2C11, and CYP3A activities by 60 to 80 percent raises the possibility of broad drug-drug interactions in chronic dosing regimens [9]. Substrates of CYP3A4 (a large fraction of marketed drugs including many statins, calcium channel blockers, immunosuppressants, and protease inhibitors), CYP1A2 (caffeine, theophylline, clozapine), and CYP2C (warfarin, phenytoin, proton pump inhibitors) could experience elevated exposure if the rat findings translate to humans. The clinical significance of these preclinical findings has not been established, but investigators conducting combination studies should consider potential elevations in exposure of co-administered drugs metabolized by these enzymes.

Other NMDA receptor modulators. Concurrent administration with other NMDA receptor antagonists (ketamine, memantine, dextromethorphan, MK-0657, nitrous oxide) would be expected to produce additive or synergistic NMDA receptor blockade. The combination of NR2B-selective and non-selective NMDA antagonists has not been studied in human research and would be expected to increase both therapeutic effects and adverse effects (dissociation, amnesia, cardiovascular effects). The combination of traxoprodil with other NR2B-selective antagonists (Ro 25-6981, rislenemdaz) has not been characterized in any model.

Antidepressants. The Poleszak et al. (2016) preclinical data demonstrated pharmacokinetic interaction between traxoprodil and several antidepressants, with increased brain concentrations of imipramine, desipramine, and escitalopram when co-administered with traxoprodil [14]. The mechanism is likely CYP-mediated inhibition of antidepressant metabolism. This interaction could contribute to both enhanced efficacy and increased adverse-event risk in combination protocols. The pharmacodynamic interaction (convergent effects on serotonergic signaling, as suggested by the p-CPA reversal experiment) may operate in parallel with the pharmacokinetic interaction [14].

QT-prolonging agents. Given the identified hERG channel inhibition liability, combination with other QT-prolonging agents (methadone, fluoroquinolones, certain antipsychotics including haloperidol and ziprasidone, citalopram, escitalopram, ondansetron at high doses, class IA and III antiarrhythmics) would increase the risk of clinically significant QTc prolongation and should be approached with caution in any research protocol. The additive QTc risk would be compounded in CYP2D6 poor metabolizers, who achieve higher traxoprodil plasma concentrations.

Dopaminergic agents. In the Parkinson's disease context, traxoprodil did not alter levodopa pharmacokinetics when co-administered intravenously [24], suggesting absence of a pharmacokinetic interaction at the level of levodopa absorption or metabolism. The pharmacodynamic interaction (potentiation of antiparkinsonian effect, modulation of dyskinesia) is the basis for the Parkinson's disease research application [12, 24].

Serotonergic agents. The partial serotonin dependence of the antidepressant-like effect of traxoprodil, demonstrated by p-CPA reversal in preclinical studies [14], suggests that the interaction with serotonergic antidepressants may involve

both pharmacokinetic (CYP inhibition) and pharmacodynamic (convergent signaling) components. The clinical significance of this convergent mechanism is unknown.

Ethanol. The Bhagwandin et al. (2020) study demonstrated neuroprotective effects of CP-101,606 against ethanol-induced neuronal damage in a developmental model [17]. The interaction between traxoprodil and ethanol in adult subjects has not been characterized. Given that both compounds modulate NMDA receptor function (ethanol is an NMDA receptor inhibitor), additive CNS depression would be anticipated.

11. Adverse Events and Safety Signal

11.1 Cardiovascular safety: QTc prolongation

The principal safety concern that led to discontinuation of traxoprodil development is QTc interval prolongation on electrocardiography, attributed to inhibition of the hERG potassium channel [30]. The hERG liability was identified as poor selectivity of the compound for NR2B-containing NMDA receptors over the hERG channel, meaning that plasma concentrations achieving therapeutic NR2B occupancy also produce clinically relevant hERG inhibition. The specific hERG IC₅₀ for traxoprodil has not been published in the peer-reviewed literature in an accessible primary source; the finding is reported in development-stage documentation and in secondary reviews that cite the QTc prolongation as the reason for program termination [30]. The hERG liability is a molecular property of the traxoprodil structure and is not a class effect of NR2B antagonists; other NR2B-selective compounds (rislenemdaz, radiprodil) do not share this liability.

The QTc concern is compounded by the CYP2D6 metabolic polymorphism, which creates unpredictable variation in plasma concentrations. CYP2D6 poor metabolizers achieve approximately two-fold higher plasma concentrations than extensive metabolizers at the same oral dose and have approximately five-fold lower clearance [8], meaning that a dose producing acceptable QTc effects in extensive metabolizers could produce dangerous QTc prolongation in poor metabolizers. The combination of hERG inhibition and CYP2D6 polymorphic metabolism represented an insurmountable safety pharmacology challenge for clinical development.

It is notable that the Nutt et al. (2008) Parkinson's disease trial, which achieved plasma concentrations of 109 and 294 ng/mL, "had no significant effects on blood pressure or on heart rate, and no significant prolongation of the QT interval was detected with EKG" [24]. The Bullock et al. (1999) open-label TBI study similarly reported "no clinically significant hematological or ECG abnormalities" [20]. The discrepancy between these small-study safety observations and the program-level QTc concern may reflect the larger sample sizes and more sensitive detection methods (thorough QT studies with baseline-corrected time-matched analysis) employed in later development-stage cardiac safety evaluation, which have greater statistical power to detect small mean QTc changes that carry population-level risk.

11.2 Dissociative and cognitive effects

The Nutt et al. (2008) Parkinson's disease study documented dose-dependent dissociative and amnesic adverse events: abnormal thinking, depersonalization, and amnesia occurred in 10 of 12 subjects at the high dose (plasma concentration 294 ng/mL) and 5 of 12 subjects at the low dose (plasma concentration 109 ng/mL) [24]. These effects are consistent with the known cognitive effects of NMDA receptor blockade and represent a class liability shared with ketamine and other NMDA antagonists. The dose-dependent nature of these effects suggests that they are pharmacologically mediated rather than idiosyncratic.

In contrast, the Preskorn et al. (2008) treatment-resistant depression trial reported that CP-101,606 was "capable of producing an antidepressant response without also producing a dissociative reaction" [23]. The discrepancy likely reflects differences in plasma concentration achieved (the depression trial used a single infusion producing lower sustained exposure than the multi-hour Parkinson's infusion protocol) and in the patient population (the depression patients were ambulatory outpatients, while the Parkinson's patients had pre-existing basal ganglia dysfunction that may increase vulnerability to NMDA-related cognitive effects). This observation suggests that a therapeutic window may exist between antidepressant efficacy and dissociative effects for NR2B-selective antagonists, in contrast to ketamine where the two effects appear more tightly coupled.

11.3 PCP-like discriminative stimulus and abuse potential

Nicholson et al. (2007) demonstrated that CP-101,606 produces PCP-like discriminative stimulus effects in rats and rhesus monkeys and serves as a reinforcer in monkey self-administration [16]. These preclinical findings indicate a nonzero abuse potential that would need to be addressed in any future clinical development program, particularly for chronic oral dosing regimens. The PCP-like discriminative stimulus is consistent with the NMDA receptor antagonist mechanism and has been observed with other NR2B-selective compounds, suggesting it is a class effect rather than specific to traxoprodil.

11.4 General tolerability across clinical trials

Across the published clinical trials, traxoprodil was generally well tolerated when administered intravenously at the studied doses and infusion rates. The Yurkewicz et al. (2005) Phase 2/3 TBI trial in 404 patients, the largest clinical safety dataset, reported no treatment-emergent safety signals that would have precluded use in this critically ill population [22]. The Preskorn et al. (2008) depression trial reported the compound as "safe" and "generally well tolerated" in ambulatory psychiatric patients [23]. The Bullock et al. (1999) open-label study reported no drug-related adverse events across all infusion durations studied [20]. Common non-serious adverse events across studies included dizziness, nausea, and somnolence, consistent with the CNS mechanism of action.

11.5 Reproductive and developmental safety

No published human reproductive or developmental safety data are available. The preclinical neuroprotection findings in the developmental ethanol model (Bhagwandin et al. 2020) suggest a favorable effect of NR2B blockade in the context of developmental neurotoxicity [17], but these findings do not constitute developmental safety data for the compound itself. The NR2B subunit is highly expressed during brain development, and modulation of NR2B-containing receptor function during critical developmental windows could have consequences for synaptogenesis and circuit maturation that have not been characterized for traxoprodil.

12. Comparative Assessment

This section presents a structured comparative assessment of five NMDA receptor-targeting or NR2B-selective compounds against traxoprodil, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators were selected to represent the principal NR2B-selective antagonists with substantive published pharmacology data and the clinically validated non-selective NMDA antagonist ketamine as a mechanistic reference.

12.1 Rislenemdaz (CERC-301, MK-0657)

Mechanism: Oral, highly selective GluN2B antagonist. Ki at human temporal cortex of 8.1 nanomolar; functional IC50 of 3.6 nanomolar; at least 1000-fold selectivity over all other tested targets [26]. Acts at the NR1/NR2B amino-terminal domain interface as an allosteric modulator [26].

Development trajectory: Originally developed by Merck as MK-0657, subsequently licensed to Cerecor as CERC-301. A pilot randomized, double-blind, placebo-controlled crossover study in 5 treatment-resistant depression patients (of 21 planned; enrollment limited by compound development discontinuation) at 4 to 8 mg/day for 12 days showed significant antidepressant effects on the Hamilton Depression Rating Scale and Beck Depression Inventory as early as day 5, but not on the primary measure (Montgomery-Asberg Depression Rating Scale) [27]. A larger Phase 2 trial (n = 137) of adjunctive CERC-301 at 8 mg daily for 28 days did not meet its primary endpoint of change in HDRS-17 at Day 7 [30]. The compound received FDA Fast Track Designation in November 2013. Phase 2 trials have been viewed as disappointing, and development activity has stalled [30].

Novelty: 3/5. Oral bioavailability distinguishes rislenemdaz from the intravenous-only traxoprodil, but the NR2B antagonist mechanism is shared.

Effect size: 2/5. Pilot study showed signals on secondary outcomes but the larger Phase 2 trial missed its primary endpoint.

Promising potential: 2/5. Development is stalled; no active trials.

Side-effect profile: 3/5. No serious or dissociative adverse effects in the pilot study [27]. The Phase 2 tolerability was acceptable.

Overall validation: 2/5. Limited positive clinical data; the principal Phase 2 trial was negative.

Comparison to traxoprodil: Rislenemdaz shares the NR2B antagonist mechanism and the depression indication but differs in route (oral versus intravenous) and clinical outcome trajectory. Traxoprodil produced a more robust antidepressant signal in the Preskorn proof-of-concept trial (60% versus 20% response rate) compared to the mixed rislenemdaz results, though the trials differed substantially in design, sample size, and route of administration. Rislenemdaz has the advantage of oral bioavailability and longer half-life (12 to 17 hours versus 2 to 4 hours in extensive metabolizers) [26]. Both compounds remain investigational.

12.2 Ifenprodil

Mechanism: First-generation NR2B-selective NMDA receptor antagonist and positive phenylethanol amine prototype. KD of approximately 60 nanomolar at NR2B [7]. Also a potent alpha-1 adrenergic receptor antagonist, sigma receptor agonist, and serotonin receptor modulator, producing significant off-target pharmacology that limits clinical utility for CNS indications.

Development trajectory: Marketed as a vasodilator and cerebral blood flow enhancer in some countries (notably Japan and France) under the trade name Cerocral. Not developed for NMDA receptor-mediated CNS indications in the United States or European Union due to the alpha-1 adrenergic liability producing hypotension.

Novelty: 2/5. The compound established the NR2B antagonist concept but is pharmacologically non-selective by modern standards.

Effect size: 2/5. Clinical efficacy as a vasodilator is established; NMDA-specific clinical efficacy has not been demonstrated in isolation from the polypharmacology.

Promising potential: 1/5. Not in active development for any NMDA receptor-related indication. Serves as a historical reference compound.

Side-effect profile: 2/5. Hypotension from alpha-1 adrenergic antagonism is the dose-limiting toxicity for CNS applications. Sedation and gastrointestinal effects are also reported.

Overall validation: 2/5. Clinically validated as a vasodilator but not as a selective NR2B antagonist.

Comparison to traxoprodil: Traxoprodil was specifically designed to eliminate the alpha-1 adrenergic activity of ifenprodil while retaining NR2B affinity. The approximately 10-fold improvement in NR2B binding affinity (KD 4 to 6 nanomolar for traxoprodil versus 60 nanomolar for ifenprodil) and the elimination of the hypotensive liability represent the core design advance [2, 7]. Ifenprodil remains useful as a pharmacological tool and structural template but is not a viable clinical comparator for NR2B-mediated indications.

12.3 Ro 25-6981

Mechanism: Highly potent and selective NR2B antagonist. IC50 of 0.009 micromolar for NR1/NR2B and 52 micromolar for NR1/NR2A, representing greater than 5000-fold selectivity [25]. Unlike traxoprodil, Ro 25-6981 maintains high-affinity binding to triheteromeric NR1/NR2A/NR2B receptors [6]. Functions as an activity-dependent blocker.

Development trajectory: Developed by Roche as a research tool. Not advanced to clinical development. Extensively used in preclinical depression, nociception, and neuroprotection research. Demonstrated antidepressant-like activity in forced swim test, sucrose preference test, and zinc-deficient animal models without hyperactivity confounds.

Novelty: 3/5. The activity-dependent mechanism and maintained binding to triheteromeric receptors distinguish it pharmacologically from traxoprodil.

Effect size: 3/5. Robust preclinical efficacy across multiple depression-relevant behavioral models, without the motor confounds seen with non-selective NMDA antagonists.

Promising potential: 2/5. No clinical development; research tool only.

Side-effect profile: 3/5. Preclinical only. Antidepressant-like actions are reported without associated hyperactivity, suggesting a favorable profile relative to non-selective antagonists.

Overall validation: 2/5. Extensively validated in preclinical models but lacks any human clinical data.

Comparison to traxoprodil: Ro 25-6981 and traxoprodil represent the two pharmacological classes of NR2B antagonists identified by Chazot et al. (2002): Ro 25-6981 binds triheteromeric receptors while traxoprodil does not [6]. This distinction means the two compounds target partially overlapping but non-identical receptor populations in the adult brain. Traxoprodil has the advantage of clinical data in humans; Ro 25-6981 has the advantage of higher selectivity and maintained binding across receptor compositions. The two compounds are complementary research tools for dissecting the contributions of diheteromeric versus triheteromeric NR2B-containing receptors to physiological and pathological processes.

12.4 Radiprodil (UCB3491)

Mechanism: Orally active negative allosteric modulator (NAM) of NR2B-containing NMDA receptors, mechanistically distinct from the competitive/allosteric antagonism of the phenylethanol amine class [28].

Development trajectory: Initially developed by Endo Pharmaceuticals for neuropathic pain, with clinical experience in 460 adult subjects (healthy volunteers and 332 neuropathic pain patients) [28]. The neuropathic pain program was terminated due to lack of efficacy, despite a favorable safety and tolerability profile at the 30 mg dose [28]. UCB subsequently acquired all rights and redirected development toward infantile spasm syndrome, exploiting the predominant expression of NR2B during early brain development. A Phase 1b pediatric study in three infants demonstrated predictable linear pharmacokinetics (half-life approximately 6.8 hours at the 0.1 mg/kg dose), no treatment-related adverse events, and no discontinuations due to adverse events [28]. Development for infantile spasms is ongoing.

Novelty: 4/5. The negative allosteric modulator mechanism and the pediatric epilepsy indication are substantially novel relative to the competitive NR2B antagonists and the adult CNS indications.

Effect size: 2/5. Failed to demonstrate efficacy in the adult neuropathic pain indication. Pediatric efficacy data are preliminary.

Promising potential: 3/5. Active development for infantile spasms with favorable pediatric safety data. The high unmet need in treatment-resistant infantile spasms supports continued development.

Side-effect profile: 4/5. The most favorable safety data in this comparator panel. No treatment-related adverse events in the pediatric Phase 1b study. The adult neuropathic pain program at 30 mg was described as "safe and well tolerated" [28].

Overall validation: 2/5. The neuropathic pain program was negative. Pediatric development is in early phases.

Comparison to traxoprodil: Radiprodil and traxoprodil target the same receptor subunit (NR2B) but through distinct allosteric mechanisms (NAM versus proton-enhancing antagonism) and for distinct indications (infantile epilepsy versus neuroprotection/depression). The comparison illustrates the breadth of therapeutic applications accessible through NR2B modulation across the lifespan. Traxoprodil has the advantage of demonstrated efficacy signals in the depression and TBI indications; radiprodil has the advantage of a cleaner safety profile and an active development program targeting an area of high unmet need.

12.5 Ketamine (and esketamine)

Mechanism: Non-selective, open-channel NMDA receptor antagonist. Blocks the ion channel pore in a use-dependent manner, requiring prior receptor activation for binding. Also acts at sigma receptors, opioid receptors, monoamine transporters, and other targets. Esketamine (the S-enantiomer) is approved by the FDA as Spravato for treatment-resistant depression [29].

Development trajectory: Zarate et al. (2006) reported the landmark randomized, placebo-controlled, crossover study demonstrating that a single intravenous infusion of ketamine (0.5 mg/kg) produced rapid antidepressant effects in 18 treatment-resistant depression patients, with a 71 percent response rate at 24 hours versus 0 percent for placebo [29]. Esketamine nasal spray (Spravato) was approved by the FDA in March 2019 for treatment-resistant depression and subsequently for major depressive disorder with acute suicidal ideation. Ketamine is also used clinically as an anesthetic, analgesic, and off-label antidepressant.

Novelty: 3/5. The ketamine antidepressant mechanism was novel when first demonstrated; the mechanism is now well-established and multiple follow-on glutamatergic antidepressants have been developed.

Effect size: 5/5. The largest antidepressant effect size in the NMDA receptor-targeting class. The 71 percent response rate at 24 hours reported by Zarate et al. (2006) and replicated in numerous subsequent studies establishes ketamine as the clinical benchmark for rapid antidepressant response [29].

Promising potential: 5/5. Esketamine is FDA-approved and commercially available. Racemic ketamine is widely used off-label.

Side-effect profile: 2/5. Significant dissociative, psychotomimetic, and hemodynamic adverse effects at antidepressant doses. Abuse potential is well-established. Requires supervised administration and post-dose monitoring. Bladder toxicity with chronic use.

Overall validation: 5/5. FDA-approved for treatment-resistant depression. Extensive clinical evidence base spanning hundreds of trials.

Comparison to traxoprodil: Ketamine and traxoprodil represent opposite ends of the selectivity spectrum for NMDA receptor-targeting antidepressants. Ketamine is non-selective, produces robust rapid antidepressant effects, and has significant dissociative and abuse-liability concerns. Traxoprodil is NR2B-selective, produced a meaningful but less dramatic antidepressant response (60% versus 20% in a small proof-of-concept trial), and notably did not produce dissociative effects at the studied dose [23]. The traxoprodil result was interpreted as evidence that NR2B-selective antagonism may capture a portion of the ketamine antidepressant mechanism with a more favorable side-effect profile. However, the subsequent failure of other NR2B-selective agents (rislenemdaz Phase 2 negative) has raised the question of whether the full antidepressant effect of ketamine requires non-selective NMDA blockade or engagement of additional pharmacological targets beyond NR2B [30].

12.6 Comparator summary

The five comparators span the pharmacological and clinical landscape of NR2B-targeted and NMDA-targeting therapeutics. **Rislenemdaz** is the closest mechanistic comparator, sharing the NR2B antagonist mechanism and the depression indication, but has not produced a positive Phase 2 trial. **Ifenprodil** is the historical prototype, limited by alpha-1 adrenergic off-target activity that traxoprodil was designed to eliminate. **Ro 25-6981** is the most pharmacologically distinct NR2B antagonist through its maintained binding to triheteromeric receptors, but remains a preclinical tool without human data. **Radiprodil** represents a novel NAM mechanism tar-

getting a different indication (infantile spasms) with a cleaner safety profile. **Ketamine/esketamine** is the clinical gold standard for rapid antidepressant response through NMDA receptor modulation, establishing the efficacy benchmark against which all NR2B-selective approaches are measured.

Traxoprodil occupies a specific position in this landscape: it is the compound that most cleanly demonstrated, in human subjects, that NR2B-selective antagonism can produce antidepressant effects without dissociative reactions, an observation that both validated the NR2B hypothesis and set the stage for subsequent NR2B antagonist development programs. Its clinical trajectory was terminated not by efficacy failure but by a cardiac safety liability (hERG/QTc) that is specific to this molecule rather than to the NR2B antagonist mechanism. The compound therefore remains informative as a proof-of-concept tool and as a benchmark for the NR2B antidepressant hypothesis, even though it is no longer itself a clinical candidate.

13. References

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