

RESEARCH MONOGRAPH . COMPOUND PROFILE

Lanicemine

A phenylethylamine NMDA channel blocker distinguished from ketamine by low channel trapping (54% versus 86%), originally developed by AstraZeneca as a neuroprotectant for acute ischaemic stroke (AR-R 15896AR), repositioned for treatment-resistant depression following the discovery of ketamine's rapid antidepressant properties, and terminated after a 302-patient Phase IIb trial failed to separate from placebo.

DOCUMENT	KDC-MN-1655
ISSUED	2026-05-22
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Low-trapping, non-competitive N-methyl-D-aspartate receptor channel blocker

ABSTRACT

Lanicemine (AZD6765, formerly AR-R 15896AR) is a low-trapping, non-competitive N-methyl-D-aspartate (NMDA) receptor channel blocker that binds within the ion channel pore of NR2A- and NR2B-containing NMDA receptor complexes with micromolar affinity (K_i 0.5 to 2.1 micromolar; IC_{50} approximately 10 micromolar at resting membrane potential in rat cortical neurons). The compound is distinguished from the prototypical NMDA channel blocker ketamine by substantially lower channel trapping (54% versus 86%), a property that confers use-dependent, voltage-dependent blockade with preferential activity on tonically active neurons and minimal psychotomimetic liability. Originally synthesized by Astra (later AstraZeneca) as a neuroprotectant designated AR-R 15896AR, the compound advanced through Phase II trials for acute ischaemic stroke in 175 and 103 patients respectively before the stroke program was terminated owing to tolerability limitations at the high doses required for neuroprotective plasma concentrations. Following the demonstration of rapid antidepressant properties of ketamine in treatment-resistant major depressive disorder by Zarate and colleagues, AstraZeneca repositioned the compound for depression under the designation AZD6765 and the International Nonproprietary Name lanicemine.

The depression clinical program comprised four principal studies. A single-infusion crossover trial at the National Institute of Mental Health ($n=22$, 150 mg intravenous) demonstrated rapid but transient antidepressant effects ($d=0.40$ on the Montgomery-Asberg Depression Rating Scale) with no psychotomimetic effects

compared to placebo. A Phase IIB repeated-dosing trial (n=152, three infusions per week for three weeks) demonstrated sustained antidepressant efficacy at 100 mg (MADRS change minus 5.5 versus placebo, p=0.006) with minimal dissociative adverse events. However, a larger Phase IIB trial (n=302, 49 centers, four countries, 15 infusions over 12 weeks) at 50 mg and 100 mg doses adjunctive to ongoing antidepressant treatment failed to separate from placebo on the primary endpoint (MADRS change at week 6) or any secondary measure, resulting in program termination by AstraZeneca in 2013.

Pharmacokinetics following intravenous administration are described by a two-compartment model with low systemic clearance (8.1 to 9.4 L/h), a terminal half-life of 10 to 16 hours, and predominantly urinary elimination (93.8% of a radiolabeled dose); the compound does not inhibit or induce CYP3A4 in vivo. Preclinical pharmacology demonstrates antidepressant-like activity in the tail suspension test (1 mg/kg, dependent on PI3K/Akt/mTOR/GSK3-beta signaling), reversal of chronic unpredictable mild stress-induced behavioral and neurometabolic deficits, and neuroprotection comparable to MK-801 in the intrastriatal malonate model without the behavioral side effects of high-trapping NMDA antagonists. The compound is positioned within a comparator landscape that includes esketamine (approved), dextromethorphan/bupropion (approved), rapastinel (Phase 3 failed), memantine (failed for depression), and rislenemdaz (pilot only). Lanicemine is not approved for any indication. It is available as a research-grade compound for in vitro and in vivo investigation; 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: Lanicemine.

Development codes: AZD6765, AZD-6765 (AstraZeneca depression program); AR-R 15896AR, ARL 15896, ARL-15896 (AstraZeneca stroke program); FPL-15896 (original Astra designation). The AR-R 15896AR designation is the canonical identifier in the stroke neuroprotection literature of the late 1990s and early 2000s [1, 2, 3]. The AZD6765 designation applies to the depression clinical program initiated in the late 2000s [4, 5, 6].

Chemical Abstracts Service registry numbers: 153322-05-5 (free base, S-enantiomer), 153322-06-6 (dihydrochloride salt), 61890-25-3 (racemic free base), 190581-71-6 (R-enantiomer free base). The S-enantiomer is the clinically studied form and the material designated by the INN lanicemine.

Database identifiers: PubChem CID 9794203 (free base); PubChem CID 9795446 (dihydrochloride); DrugBank DB11889; IUPHAR/BPS Guide to Pharmacology Ligand 7681.

1.2 Structural class and chemistry

Lanicemine is a phenylethylamine derivative bearing a pyridin-2-yl substituent on the ethylamine backbone. The compound belongs to the broad structural class of arylethylamines that includes phencyclidine and ketamine as NMDA channel blockers, although lanicemine is substantially smaller and simpler in structure than either of those prototypical agents. The molecular scaffold consists of a phenyl ring, a two-carbon ethylamine bridge, and a pyridine ring; the single chiral center at C1 of the ethanamine backbone defines the S-enantiomer (active, clinically studied) and R-enantiomer (less active).

International Union of Pure and Applied Chemistry name: (1S)-1-phenyl-2-(pyridin-2-yl)ethanamine.

Molecular formula: C₁₃H₁₄N₂ (free base); C₁₃H₁₆Cl₂N₂ (dihydrochloride salt).

Molecular weight: 198.26 g/mol (free base); 271.19 g/mol (dihydrochloride salt).

Exact mass: 198.1157 g/mol (free base, monoisotopic).

Physical properties: The dihydrochloride salt is a white to off-white crystalline powder. It is soluble in water and in common polar organic solvents (methanol, dimethyl sulfoxide). The free base is soluble in organic solvents and sparingly soluble in water at neutral pH.

Stereochemistry: Lanicemine contains a single stereocenter at C1 of the ethanamine bridge. The S-enantiomer is the pharmacologically active and clinically studied form; the R-enantiomer (CAS 190581-71-6) has been prepared for stereochemical comparison but has not been advanced clinically. Research-grade lanicemine is supplied as the S-enantiomer dihydrochloride salt at greater than 97% chemical purity by high-performance liquid chromatography [7]. Investigators should confirm enantiomeric identity by chiral chromatography or optical rotation.

1.3 Synthesis

The original synthesis of AR-R 15896AR proceeded through standard organic chemistry routes at Astra's research laboratories. A more recent chemoenzymatic synthesis has been described by Borowiecki and Bretner (2019), who reported highly efficient asymmetric bioreduction of 1-aryl-2-(azaaryl)ethanone precursors using ketoreductases (KREDs) to produce the corresponding chiral secondary alcohols with enantiomeric excesses exceeding 99%, followed by amination to yield lanicemine in optically pure form [8]. The absolute configuration of the products was assigned by modified Mosher and Kelly methods. AstraZeneca holds US Patent Application 20120277272 A1 (published 2012), titled "Ethanamine Compounds and Methods of Using the Same," which covers lanicemine and structurally related ethanamine NMDA channel blockers [9].

3. Discovery and Development History

3.1 Origin and neuroprotection program

Lanicemine was originally synthesized at Astra (subsequently AstraZeneca following the 1999 merger) under the designation FPL-15896, later AR-R 15896AR, as part of a program to develop low-affinity, use-dependent NMDA receptor antagonists for neuroprotection in acute ischaemic stroke. The rationale was that high-affinity NMDA antagonists such as MK-801 (dizocilpine) provided robust neuroprotection in animal models but were limited clinically by severe psychotomimetic, cardiovascular, and neurobehavioral side effects; lower-affinity compounds with use-dependent kinetics were hypothesized to provide neuroprotection selectively at pathologically overactive NMDA receptors while preserving normal synaptic function [2, 10].

Greene, Porter, and Greenamyre (1996) published the first detailed pharmacological characterization of ARL-15896, demonstrating that it was a low-affinity NMDA channel blocker approximately 3000-fold less potent than MK-801 at displacing [3H]MK-801 binding, with regional IC₅₀ values of 17 micromolar in the cerebellum and 45 micromolar in the forebrain [1]. In the intrastriatal malonate excitotoxicity model in rats, ARL-15896 at 9.0 mg/kg subcutaneously reduced lesion volume by 80%, a degree of protection comparable to MK-801 but without the behavioral side effects observed with the high-trapping compound [1].

Palmer and colleagues (1999) reviewed the expanded preclinical data and reported that AR-R 15896AR had advanced to Phase II trials for stroke, with demonstrated neuroprotection across multiple in vivo and in vitro ischaemia and excitotoxicity models [2].

3.2 Clinical development for stroke

Two clinical trials of AR-R 15896AR in acute ischaemic stroke were completed. Lees and colleagues (2001) reported a four-part, multicenter, randomized, double-blind, placebo-controlled dose-ranging study in 175 patients (mean age 69 years) enrolled within 24 hours of stroke symptom recognition [3]. Ascending loading doses of 100 to 300 mg intravenous over 60 minutes were examined, with maintenance doses of

60 to 120 mg every 8 hours. The maximum tolerated loading infusion was 250 mg; steady-state plasma concentrations after nine maintenance doses of 120 mg were 1847 plus or minus 478 ng/mL. Mortality and serious adverse event rates were comparable between drug and placebo groups (9% versus 11% mortality; 23% versus 33% SAEs). Adverse events associated with the compound were dizziness, vomiting, nausea, stupor, and agitation/hallucination, with treatment withdrawal rates increasing dose-dependently (7% placebo, 12% at 250 mg, 20% at 300 mg) [3].

Diener and colleagues (2002) conducted a higher-dose safety study at 19 centers in France, Germany, and the Netherlands in 103 acute ischaemic stroke patients randomized to AR-R 15896AR (n=70) or placebo (n=33) [4]. Loading doses of 3.5 mg/kg were followed by maintenance infusions of 120 mg every 8 hours for 3 days. Active treatment produced more adverse events than placebo: vomiting (29% versus 9%), nausea (23% versus 12%), fever (17% versus 12%), agitation (7% versus 3%), dizziness (7% versus 0%), and hallucinations (6% versus 0%). Three psychiatric serious adverse events occurred in the active group versus none in placebo. The stroke program was terminated following these tolerability findings at the high plasma concentrations required for neuroprotection [4].

3.3 Repositioning for depression

Following the landmark demonstration by Zarate and colleagues (2006) that a single intravenous infusion of ketamine (0.5 mg/kg) produced rapid antidepressant effects in treatment-resistant major depressive disorder, AstraZeneca recognized that its low-trapping NMDA channel blocker might replicate ketamine's antidepressant mechanism at substantially lower psychotomimetic risk [11]. The compound was redesignated AZD6765 and subsequently received the International Nonproprietary Name *lanicemine*.

3.4 Depression clinical program and termination

The depression clinical program comprised Phase I pharmacokinetic and quantitative electroencephalography studies in healthy volunteers, followed by four Phase II efficacy studies in major depressive disorder. The principal studies were: a NIMH crossover trial of single 150 mg infusion in 22 treatment-resistant patients (Zarate et al. 2013) [5]; a Phase IIA single-infusion study of 100 mg in 34 patients [6]; a Phase IIB repeated-dosing study of 100 mg and 150 mg in 152 patients with three infusions per week for three weeks (Sanacora et al. 2013) [6]; and a large Phase IIb adjunctive

study of 50 mg and 100 mg in 302 patients at 49 centers across four countries with 15 infusions over 12 weeks (Sanacora et al. 2017) [12]. The first three studies showed signals of antidepressant efficacy with minimal psychotomimetic effects; the fourth, pivotal study failed to separate from placebo on the primary or any secondary endpoint, resulting in program termination by AstraZeneca in 2013 [12]. The compound is not approved by any regulatory authority for any indication. No subsequent commercial sponsor has advanced lanicemine into new clinical trials for depression or other psychiatric indications.

4. Molecular Pharmacology

4.1 NMDA receptor channel blockade

The N-methyl-D-aspartate receptor is a heterotetrameric ligand-gated ion channel of the ionotropic glutamate receptor superfamily, composed of two obligatory GluN1 subunits and two GluN2 (GluN2A, GluN2B, GluN2C, or GluN2D) or GluN3 subunits. The receptor requires simultaneous binding of glutamate and the co-agonist glycine (or D-serine) for activation, and is further regulated by voltage-dependent magnesium block at resting membrane potential, by zinc, by polyamines, and by redox state. It is expressed broadly throughout the central nervous system, with particular density in cortical and hippocampal circuits relevant to mood, cognition, and synaptic plasticity.

Lanicemine binds within the ion channel pore of NMDA receptor complexes containing NR2A and NR2B subunits, producing non-competitive, use-dependent, voltage-dependent antagonism [1, 2, 10]. The compound is nonselective between NR2A and NR2B subtypes. The binding affinity is in the low micromolar range: K_i values of 0.56 to 2.1 micromolar have been reported across assay systems, with IC_{50} values of 4 to 40 micromolar depending on membrane potential, species, and assay configuration [1, 6, 10].

In quantitative receptor autoradiography of rat brain sections, Greene and colleagues (1996) demonstrated that ARL-15896 displaced [3H]MK-801 binding with IC_{50} values of 17 micromolar in the cerebellum and 45 micromolar in the forebrain, approximately 3000-fold lower affinity than MK-801 in all brain regions examined [1]. In patch-clamp electrophysiology on rat cortical neuron cultures, the compound inhibited NMDA (50 micromolar)-evoked currents at negative 60 mV with an IC_{50} of approximately 9.8 micromolar [10]. The K_D values were voltage-dependent: approximately 60 micromolar at 0 mV and 11 micromolar at negative 60 mV, consistent with deeper channel penetration and stronger block at hyperpolarized potentials [10].

4.2 Use dependence and low trapping

Two mechanistic properties distinguish lanicemine from higher-affinity NMDA channel blockers. First, the antagonism is use-dependent: application of the compound 60 seconds before NMDA receptor activation did not attenuate the initial NMDA-evoked current, although blockade developed rapidly once the channel opened [10]. This property implies that lanicemine preferentially blocks channels that are already open (pathologically overactive neurons) rather than resting channels, providing a pharmacological basis for selective action on tonically active circuits.

Second, and more distinctively, lanicemine exhibits low channel trapping. Sanacora and colleagues (2013) reported that lanicemine produces 54% channel trapping compared with 86% for ketamine, based on electrophysiological measurements of the fraction of blocker that remains within the channel after agonist washout [6]. Low trapping means that lanicemine dissociates from the closed channel more readily than ketamine, allowing faster recovery of normal NMDA receptor function after the pathological stimulus subsides. The trapping difference is the principal pharmacological basis for the reduced psychotomimetic and dissociative liability of lanicemine relative to ketamine [6, 13].

The functional consequence is a selectivity window: lanicemine preferentially blocks neurons with sustained, tonic NMDA receptor activation (such as cortical GABAergic interneurons under conditions of excitotoxic or inflammatory glutamate excess) while relatively sparing neurons with normal, phasic NMDA receptor activity [6]. This selective cortical disinhibition was demonstrated by quantitative electroencephalography in a Phase I study in healthy volunteers, where lanicemine at 75, 100, and 150 mg intravenous produced dose-dependent increases in gamma-band power (a marker of cortical disinhibition through interneuron blockade) comparable to those produced by ketamine at 0.5 mg/kg, without the ketamine-associated increases in dissociative symptoms (Clinician-Administered Dissociative States Scale) [6].

4.3 Downstream signaling pathways

The antidepressant-like effects of lanicemine depend on the PI3K/Akt/mTOR/GSK3-beta signaling cascade, a pathway shared with ketamine. Neis and colleagues (2020) demonstrated that a single administration of AZD6765 at 1 mg/kg intraperitoneally in female mice produced an antidepressant-like effect in the tail suspension test

that was abolished by intracerebroventricular pretreatment with the PI3K inhibitors LY294002 (10 nmol/site) and wortmannin (0.1 microgram/site) and by the mTOR inhibitor rapamycin (0.2 nmol/site) [14]. Furthermore, co-administration of a sub-effective dose of AZD6765 (0.1 mg/kg) with the non-selective GSK3-beta inhibitor lithium chloride (10 mg/kg oral) or the selective GSK3-beta inhibitor AR-A014418 (0.01 microgram/site intracerebroventricular) produced a synergistic antidepressant-like effect [14]. The same study demonstrated that AZD6765 increased synapsin I immunocontent in the prefrontal cortex within 30 minutes of administration, consistent with rapid enhancement of synaptic vesicle function; however, P70S6K phosphorylation and GluA1 subunit levels were not significantly altered, suggesting selective engagement of specific downstream effectors rather than global activation of the mTOR signaling cascade [14].

4.4 Neuroimaging correlates

Downey and colleagues (2016) investigated the neural correlates of lanicemine and ketamine action in 60 unmedicated adults with major depressive disorder using pharmacological functional magnetic resonance imaging during 60-minute constant intravenous infusions [15]. Both ketamine and lanicemine produced activation (not deactivation) of the anterior cingulate cortex, and this activation predicted mood improvement at 1 and 7 days post-infusion [15]. The finding that two mechanistically related NMDA channel blockers with differing trapping properties both activated the ACC suggests that anterior cingulate modulation represents a shared antidepressant mechanism for this compound class, rather than an artifact of the dissociative or psychotomimetic effects that distinguish ketamine from lanicemine [15].

4.5 Composite pharmacology

The composite pharmacology of lanicemine at the doses studied in depression trials (50 to 150 mg intravenous, producing peak plasma concentrations of approximately 1.5 micrograms per milliliter at steady state) [16] places the compound at low micromolar free plasma concentrations, within the range of its NMDA channel blocking potency. The principal molecular consequence at these concentrations is preferential blockade of tonically active NMDA receptors, cortical disinhibition through GABAergic interneuron blockade, downstream activation of PI3K/Akt/mTOR signaling, and enhancement of synaptic protein expression and synaptic plasticity in prefrontal and cingulate circuits relevant to mood regulation.

5. Pharmacokinetics and Routes of Administration

5.1 Route of administration

Lanicemine has been administered intravenously in all published clinical efficacy studies, typically as a 60-minute infusion at doses of 50 to 150 mg. An oral formulation was studied in a Phase I single ascending dose/multiple ascending dose study (NCT00963365), but results from the oral program have not been published in peer-reviewed form, and the clinical development was conducted entirely with the intravenous formulation [12].

5.2 Pharmacokinetic model

Agbo, Bui, and Zhou (2017) conducted a population pharmacokinetic analysis of 2531 plasma lanicemine concentrations from 191 healthy subjects and patients with major depressive disorder across four clinical studies [17]. The pharmacokinetics following intravenous infusion were best described by a two-compartment model with zero-order input and first-order elimination. Parameter estimates were: systemic clearance (CL) 9.43 L/h (90% CI 9.12 to 9.77), central compartment volume of distribution (V1) 106 L (90% CI 93.7 to 115), peripheral volume of distribution (V2) 47.3 L (95% CI 39.6 to 56.6), and intercompartmental clearance (Q) 75.7 L/h (90% CI 51.8 to 127) [17]. Lean body mass and body surface area were identified as statistically significant covariates affecting CL and V1, respectively; sex, race, age, body weight, laboratory measures, and concomitant medications did not significantly influence the pharmacokinetics [17].

5.3 Clearance and half-life

Lanicemine is a low-clearance compound. Three independent estimates of systemic clearance converge: 9.43 L/h from the population pharmacokinetic analysis [17], 8.1 L/h from the midazolam interaction study at steady state after 150 mg daily for 6 days [16], and 8.3 L/h from the radiolabeled ADME study [18]. The terminal elimination half-life has been reported as 10.4 hours at steady state following re-

peated 150 mg daily dosing [16] and 16 hours following a single 150 mg infusion in the radiolabeled ADME study [18]; the difference likely reflects the contribution of distribution phases and the context of single versus repeated dosing.

5.4 Distribution

The volume of distribution at steady state is approximately 106 to 122 L, consistent with moderate extravascular distribution [16, 17]. The compound crosses the blood-brain barrier; central nervous system penetration is demonstrated by the pharmacological effects observed in clinical studies (gamma-band EEG changes, anterior cingulate activation on fMRI) [6, 15]. Plasma protein binding data have not been published in the peer-reviewed literature.

Peak plasma concentrations following a single 150 mg intravenous infusion over 60 minutes reached approximately 1.51 micrograms per milliliter at steady state [16]. In the stroke dose-ranging study, plasma concentrations at the end of a 250 mg loading infusion were 1524 plus or minus 536 ng/mL, and steady-state concentrations after nine maintenance doses of 120 mg every 8 hours were 1847 plus or minus 478 ng/mL [3].

5.5 Metabolism and excretion

Guo and colleagues (2015) conducted a definitive human ADME study in six healthy male subjects following a single 150 mg intravenous infusion of [14C]-lanicemine [18]. Lanicemine was the major circulating component, representing 84% of peak radioactivity (C_{max}) and 66% of total radioactivity exposure (AUC), with a half-life of 16 hours [18]. The mean recovery of radioactivity from urine was 93.8% of the administered dose, establishing urinary excretion as the predominant elimination pathway [18].

Ten metabolites were identified in urine. The most abundant was an O-glucuronide conjugate (M1), accounting for approximately 11% of the dose in excreta [18]. Circulating metabolites identified in plasma were a para-hydroxylated metabolite (M1), an O-glucuronide (M2), an N-carbamoyl glucuronide (M3), and an N-acetylated metabolite (M6); each accounted for less than 4% of total plasma or urine radioactivity [18]. The metabolic profile is predominantly Phase II (glucuronidation) rather than Phase I (oxidative), with the parent compound dominating systemic exposure.

5.6 Drug-drug interactions

Bui and colleagues (2015) evaluated the effect of multiple intravenous doses of lanicemine (150 mg daily for 6 days) on the pharmacokinetics of the CYP3A substrate midazolam (5 mg oral) in 46 healthy volunteers in an open-label, fixed-sequence study [16]. The geometric least-squares mean ratios and 90% confidence intervals for midazolam AUC and C_{max} were within the 80% to 125% bioequivalence limits, demonstrating that lanicemine has no clinically significant effect on CYP3A4 activity [16]. No formal studies of CYP2D6, CYP1A2, or CYP2C19 interactions have been published. Given the predominantly glucuronidation-based metabolic pathway, clinically significant cytochrome P450-mediated drug-drug interactions are unlikely, although this has not been comprehensively characterized.

6. Preclinical Pharmacology

6.1 Neuroprotection

The initial preclinical characterization of ARL-15896 focused on neuroprotection in excitotoxicity and ischaemia models. Greene, Porter, and Greenamyre (1996) demonstrated that ARL-15896 reduced the volume of striatal lesions produced by the mitochondrial toxin malonate (a competitive inhibitor of succinate dehydrogenase whose toxicity is mediated largely by the NMDA receptor) by 80% when administered either intrastriatally (200 nmol) or subcutaneously (9.0 mg/kg) in Sprague-Dawley rats [1]. This degree of protection was comparable to that reported for MK-801. Critically, and in contrast to MK-801, administration of ARL-15896 was not associated with any apparent behavioral side effects [1]. The compound was also effective when administered after the malonate injection, supporting a therapeutic window for post-insult intervention [1].

Palmer and colleagues (1999) reviewed additional neuroprotection data and confirmed efficacy across multiple *in vivo* and *in vitro* ischaemia models, including transient middle cerebral artery occlusion in rats [2]. The neuroprotective profile was attributed to the use-dependent mechanism: preferential blockade of pathologically overactive NMDA receptors in the ischaemic penumbra while sparing physiological NMDA receptor function in unaffected brain regions [2].

6.2 Antidepressant-like activity

Neis and colleagues (2020) provided the most detailed mechanistic characterization of lanicemine's antidepressant-like effects in mice [14]. A single administration of AZD6765 at 1 mg/kg intraperitoneally produced a significant antidepressant-like effect in the tail suspension test in female mice [14]. This effect was dependent on the PI3K/Akt/mTOR/GSK3-beta signaling cascade, as demonstrated by reversal with the reversible PI3K inhibitor LY294002, the irreversible PI3K inhibitor wortmannin, and the mTOR inhibitor rapamycin [14]. A sub-effective dose of AZD6765 (0.1 mg/kg) produced synergistic antidepressant-like effects when combined with GSK3-beta inhibitors (lithium chloride 10 mg/kg oral; AR-A014418 0.01 microgram/site intracerebroventricular), establishing GSK3-beta as a convergent

target [14]. At 3 mg/kg, AZD6765 was active in the novelty-suppressed feeding test, a paradigm sensitive to chronic but not acute conventional antidepressant treatment [14]. The molecular correlate was an increase in synapsin I immuncontent in the prefrontal cortex at 30 minutes post-administration, while P70S6K phosphorylation and GluA1 receptor subunit levels were not significantly changed [14].

6.3 Chronic stress models

Mishra and colleagues (2020) evaluated lanicemine in a chronic unpredictable mild stress (CUMS) model of depression in male C57BL/6 mice subjected to three weeks of CUMS [19]. Stressed mice exhibited significantly reduced sucrose preference (anhedonia) and increased immobility in the forced swim test. Lanicemine treatment reversed both behavioral measures [19]. Using proton-observed carbon-edited magnetic resonance spectroscopy with isotope tracers, the investigators demonstrated that CUMS impaired glucose oxidation in both glutamatergic and GABAergic neurons in the prefrontal cortex, and that lanicemine restored these metabolic rates, providing a neurometabolic correlate for the behavioral rescue [19].

6.4 Comparison to R-ketamine in social defeat stress

Qu and colleagues (2017) directly compared lanicemine (10 mg/kg intraperitoneally) and R-ketamine (10 mg/kg intraperitoneally) in susceptible C57BL/6 male mice following 10 days of chronic social defeat stress [20]. R-ketamine produced robust antidepressant effects, significantly reducing immobility in the tail suspension and forced swim tests and showing potent anti-anhedonia effects two days after a single dose [20]. Lanicemine, at the same dose, produced no measurable antidepressant response in this model [20]. Furthermore, R-ketamine substantially restored the altered gut microbiota composition (attenuating reduced Bacteroidales and Clostridiales levels), while lanicemine showed minimal effects on most bacterial taxa [20]. The negative lanicemine result in this model is consistent with the clinical failure in the larger Phase IIb trial and suggests that the low-trapping mechanism, while reducing psychotomimetic liability, may also reduce the antidepressant efficacy that appears to depend on a certain threshold of NMDA receptor blockade [20].

6.5 Combination with hyperforin

Pochwat and colleagues (2022) tested lanicemine in combination with hyperforin (the principal bioactive constituent of *Hypericum perforatum*) in a treatment-resistant depression model combining chronic restraint stress with dietary zinc restriction in C57BL/6J mice [21]. In this model, ketamine and imipramine individually failed to restore behavioral deficits, establishing treatment resistance [21]. However, the combination of hyperforin (2.5 mg/kg) and lanicemine (10 mg/kg) intraperitoneally restored the depression-like behavioral phenotype and normalized dendritic spine morphology in the hippocampus [21]. The finding suggests that lanicemine may retain therapeutic potential in combination approaches that complement its NMDA channel blocking mechanism with additional pharmacological targets.

7. Clinical Evidence Base

The following section summarizes clinical evidence for research context. Lanicemine is not approved for any indication by any regulatory authority. This information is provided for research use only and does not constitute a recommendation for therapeutic application.

7.1 NIMH single-infusion crossover trial

Zarate and colleagues (2013) conducted a double-blind, randomized, crossover, placebo-controlled study at the National Institute of Mental Health in 22 subjects with DSM-IV treatment-resistant major depressive disorder [5]. Subjects received a single intravenous infusion of either AZD6765 (150 mg) or saline placebo on two test days one week apart. Montgomery-Asberg Depression Rating Scale (MADRS) scores improved significantly within 80 minutes of infusion (p less than 0.05) and remained significant through 110 minutes, with an effect size of $d=0.40$ [5]. On the Hamilton Depression Rating Scale (HAM-D), significant drug-placebo differences were observed at 80 and 110 minutes and at Day 2, with an effect size of $d=0.49$ [5]. Overall, 32% of subjects responded to AZD6765 and 15% responded to placebo at some point during the trial [5]. Critically, no difference was observed between groups with regard to psychotomimetic or dissociative adverse effects, establishing the separation between antidepressant efficacy and psychotomimetic liability that motivated the subsequent clinical program [5].

7.2 Phase I quantitative EEG study

Sanacora and colleagues (2013) reported a randomized, double-blind, four-way crossover study in 23 healthy male volunteers (ages 30 to 45) who received single 60-minute intravenous infusions of lanicemine at 75, 100, and 150 mg and ketamine at 0.5 mg/kg, with quantitative EEG and Clinician-Administered Dissociative States Scale (CADSS) assessments [6]. Ketamine significantly increased CADSS scores at 1 hour (p less than 0.01); lanicemine produced no significant increase at any dose [6]. Dissociative adverse events occurred in 7% at 75 mg, 11% at 150 mg, and 24% with ketamine [6]. The EEG data were used to establish dose equivalence between lan-

icemine and ketamine based on gamma-band power increases, confirming that the two compounds produce comparable cortical disinhibition at functionally equivalent brain concentrations despite the marked difference in dissociative liability [6].

7.3 Phase IIA single-infusion study (Study 1, NCT00491686)

A Phase IIA randomized, double-blind study enrolled 34 treatment-resistant MDD patients (16 lanicemine, 18 placebo) who received a single 100 mg intravenous infusion [6]. The primary endpoint, MADRS change at 24 hours, was not significant. A trend toward improvement was observed at 72 hours (minus 5.7 MADRS points versus placebo, $p=0.089$) [6].

7.4 Phase IIB repeated-dosing study (Study 9, NCT00781742)

Sanacora and colleagues (2013) reported the pivotal repeated-dosing study in 152 outpatients with moderate-to-severe major depressive disorder and history of poor antidepressant response, randomized to three intravenous infusions per week for three weeks (non-consecutive days) of lanicemine 100 mg ($n=51$), lanicemine 150 mg ($n=51$), or saline placebo ($n=50$), following a single-blind saline run-in period [6]. At the week 3 primary endpoint:

The 100 mg dose produced a MADRS change of minus 5.5 points versus placebo (95% CI minus 9.1 to minus 1.9, $p=0.006$) [6]. The 150 mg dose produced a MADRS change of minus 4.8 points versus placebo (95% CI minus 8.5 to minus 1.2, $p=0.019$) [6]. The response rate (50% or greater MADRS reduction) was 37% at 100 mg versus 16% with placebo (odds ratio 3.34, $p=0.014$) [6]. The remission rate (MADRS 10 or less) was 20% at 100 mg versus 10% with placebo (odds ratio 2.20, $p=0.186$) [6]. Dizziness was the most common adverse event (49% at 100 mg, 37% at 150 mg, versus 12% placebo) [6]. Dissociative adverse events occurred in 6% (100 mg) and 10% (150 mg) versus 0% placebo [6]. The antidepressant effect was sustained during a 5-week treatment-free follow-up period, suggesting a disease-modifying rather than purely symptomatic effect [6].

7.5 Phase IIb adjunctive study (NCT01482221)

The largest and definitive study was a Phase IIb, randomized, parallel-arm, double-blind, placebo-controlled trial conducted at 49 centers in four countries between December 2011 and August 2013 (Sanacora et al. 2017) [12]. A total of 302 patients aged 18 to 70 years with single-episode or recurrent MDD and a history of inadequate treatment response were randomized equally to receive 15 double-blind intravenous infusions of adjunctive lanicemine 50 mg, lanicemine 100 mg, or saline over a 12-week course, in addition to ongoing antidepressant therapy [12]. The primary efficacy endpoint was change in MADRS total score from baseline to week 6; secondary endpoints included MADRS change to week 12, response and remission rates, Clinical Global Impression scale, Quick Inventory of Depressive Symptomatology Self-Report, and Sheehan Disability Scale [12].

Of 302 randomized patients, 240 (79.5%) completed treatment. Neither the 50 mg nor 100 mg dose was superior to placebo on the primary endpoint or any secondary measure [12]. There was no significant difference between lanicemine and placebo treatment on any outcome measure related to MDD [12]. The compound was generally well tolerated [12]. This negative result led to termination of the depression program by AstraZeneca.

7.6 Neuroimaging study

Downey and colleagues (2016) conducted a randomized, double-blind, placebo-controlled pharmacological fMRI study in 60 unmedicated adults with major depressive disorder, comparing lanicemine and ketamine infusions [15]. Both compounds activated the anterior cingulate cortex, and this activation predicted subsequent mood improvement at days 1 and 7, suggesting a shared neural substrate for the antidepressant mechanism of NMDA channel blockers [15]. Neither drug showed significant acute antidepressant effects versus placebo in this particular study, which was designed for mechanism rather than efficacy assessment [15].

7.7 PTSD proof-of-mechanism protocol

Lijffijt and colleagues (2019) published a protocol for a randomized, placebo-controlled Phase 1b proof-of-mechanism study testing lanicemine in individuals with symptoms of post-traumatic stress disorder (CAPS-5 score 25 or greater) and evidence of behavioral sensitization [22]. Twenty-four subjects were to receive three

100 mg intravenous infusions over 5 non-consecutive days, with anxiety-potentiated startle as the primary endpoint and EEG biomarkers as secondary measures [22]. As of the present monograph date, results from this study have not been published in a peer-reviewed forum.

7.8 Additional registered studies

The ADME study (NCT01217645) assessed the distribution, metabolism, and excretion of [14C]-lanicemine after single-dose intravenous administration in healthy volunteers [18]. An oral single ascending dose/multiple ascending dose study (NCT00963365) was registered but results have not been published. The complete ClinicalTrials.gov registry for AZD6765 includes additional Phase I pharmacokinetic and safety studies (NCT01069822, NCT00785915, NCT01130909) whose results are incorporated into the published population pharmacokinetic analysis [17].

8. Sourcing and Quality Verification

Lanicemine is not approved for clinical use in any jurisdiction. The following information pertains to research-grade material for in vitro and in vivo investigation. Investigators should obtain analytical confirmation of identity and purity on every lot.

Research-grade lanicemine is available from multiple chemical and pharmaceutical research suppliers. Sigma-Aldrich (catalog SML0635) supplies lanicemine as the free base at 97% or greater purity by HPLC [7]. MedChemExpress supplies both the free base and the dihydrochloride salt at 98% or greater purity. Cayman Chemical (catalog 9002129), BOC Sciences, and additional specialty chemical suppliers also offer the compound in milligram to gram quantities.

The compound is supplied as a white to off-white solid (free base or dihydrochloride salt). The dihydrochloride salt (CAS 153322-06-6, MW 271.19) is the more common supply form for aqueous dissolution. The free base (CAS 153322-05-5, MW 198.26) is available for organic solvent applications.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98%
- Mass spectrometry confirmation of molecular weight (199.12 for the protonated free base $[M+H]^+$; 272.07 for the protonated dihydrochloride $[M+H]^+$ after salt correction)
- Chiral HPLC or optical rotation confirmation that the material is the S-enantiomer (CAS 153322-05-5), since the racemic form (CAS 61890-25-3) and R-enantiomer (CAS 190581-71-6) are also commercially available and would produce different pharmacological profiles
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Residual solvent analysis if the intended application is parenteral research

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade lanicemine market is modest but established; supply is consistent across multiple vendors.

9. Reconstitution and Handling

Lanicemine dihydrochloride is soluble in water at concentrations suitable for research applications. For in vitro work, stock solutions are typically prepared at 10 to 50 mM in dimethyl sulfoxide (DMSO) or water, aliquoted, and stored at minus 20 degrees Celsius. For in vivo injectable applications, the compound is dissolved in sterile normal saline at the required concentration (typically 1 to 15 mg/mL based on published animal dosing studies at 1 to 10 mg/kg) and administered intraperitoneally or intravenously.

In clinical studies, lanicemine was administered as an intravenous infusion over 60 minutes at concentrations of 50 to 150 mg diluted in saline [5, 6, 12]. The specific pharmaceutical formulation details (vehicle composition, stability data, compounding specifications) for the clinical-grade material have not been published; investigators conducting research with research-grade material should prepare solutions fresh or within validated stability windows.

Storage of the solid compound at minus 20 degrees Celsius under desiccation is recommended for long-term stability. Aqueous stock solutions should be used within 24 hours of preparation unless stability data for the specific solvent system are available. Freeze-thaw cycling should be minimized; aliquoting of stock solutions for single use is recommended. The compound is not known to be light-sensitive, but protection from light during storage is reasonable practice.

10. Stack Interaction Considerations

Lanicemine interacts with other compounds through its NMDA receptor pharmacology and through potential pharmacokinetic overlaps. Investigators conducting research with lanicemine in combination with other compounds should consider:

Other NMDA receptor modulators: Concurrent administration with ketamine, esketamine, memantine, dextromethorphan, or other NMDA channel blockers produces additive or overlapping channel blockade. The combination is pharmacologically redundant and may exceed the threshold for psychotomimetic effects that lanicemine alone does not produce. In the preclinical literature, R-ketamine and lanicemine have been compared but not combined [20]; combination studies would require careful dose-response characterization.

Glutamate-modulating agents: Compounds that increase synaptic glutamate (such as N-acetylcysteine acting through the cystine-glutamate antiporter, or glutamate release modulators) may alter the pharmacodynamic context for NMDA channel blockade. The lamotrigine-lanicemine interaction has not been studied but is mechanistically plausible (lamotrigine reduces glutamate release, potentially reducing the tonic NMDA receptor activity on which lanicemine's use-dependent mechanism depends).

Antidepressants: In the Phase IIb adjunctive study, lanicemine was administered concurrently with ongoing antidepressant therapy (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and other standard agents) without evidence of pharmacokinetic interaction or unexpected pharmacodynamic toxicity [12]. The lack of CYP3A4 inhibition or induction [16] and the predominantly glucuronidation-based metabolic pathway suggest low risk for pharmacokinetic interactions with antidepressants.

CYP3A4 substrates and inhibitors: Lanicemine does not inhibit or induce CYP3A4, as demonstrated by the negative midazolam interaction study [16]. Whether lanicemine is itself a substrate of CYP3A4 or other cytochrome P450 enzymes has not been published; the metabolic profile is dominated by glucuronidation [18].

GSK3-beta inhibitors: Lithium chloride produced synergistic antidepressant-like effects with sub-effective doses of lanicemine in the mouse tail suspension test [14]. This preclinical interaction is mechanistically coherent (convergence on the PI3K/Akt/GSK3-beta pathway) and suggests that lithium-lanicemine combinations may be of research interest, although no clinical combination data exist.

Hyperforin-containing preparations: The hyperforin-lanicemine combination restored behavioral deficits in a treatment-resistant mouse model where each compound alone was insufficient [21]. Hyperforin is a TRPC6 channel activator and multimodal pharmacological agent; the mechanistic basis for the synergy with lanicemine has not been fully characterized.

QT-prolonging agents: No QT prolongation signal has been identified with lanicemine in published clinical data, but formal thorough QT studies have not been published. Caution with concurrent QT-prolonging agents is reasonable pending definitive data.

11. Adverse Events and Safety Signal

11.1 Adverse events in depression trials

Across the depression clinical program, lanicemine was generally well tolerated at the studied doses of 50 to 150 mg intravenous. The most common adverse event in the Phase IIB repeated-dosing study (Study 9) was dizziness, occurring in 49% of patients receiving 100 mg, 37% receiving 150 mg, and 12% receiving placebo [6]. Dissociative adverse events occurred in 6% (100 mg) and 10% (150 mg) versus 0% with placebo [6]. In the same study, CADSS scores (the standard measure of dissociative symptoms) showed no significant increase with lanicemine, in contrast to ketamine which produced significant CADSS elevation at 1 hour (p less than 0.01) [6].

In the larger Phase IIB study (n=302), the investigators reported that lanicemine was "generally well tolerated" at both 50 mg and 100 mg, with no new safety signals identified beyond those observed in earlier studies [12]. Completion rates were 79.5% (240 of 302), comparable across treatment arms [12].

In the NIMH crossover trial, no difference was observed between AZD6765 and placebo groups with regard to psychotomimetic or dissociative adverse effects [5].

11.2 Adverse events in stroke trials

At the substantially higher doses required for neuroprotective plasma concentrations in stroke, AR-R 15896AR produced a more pronounced adverse event profile. Lees and colleagues (2001) reported adverse events of dizziness, vomiting, nausea, stupor, and agitation/hallucination at loading doses of 250 to 300 mg [3]. Treatment withdrawals increased dose-dependently: 7% with placebo, 12% at 250 mg, and 20% at 300 mg [3]. Mortality and serious adverse event rates were comparable between drug and placebo groups [3].

Diener and colleagues (2002) reported more substantial tolerability issues at higher doses (3.5 mg/kg loading followed by 120 mg maintenance every 8 hours for 3 days): vomiting (29% versus 9% placebo), nausea (23% versus 12%), fever (17% versus 12%), agitation (7% versus 3%), dizziness (7% versus 0%), and hallucinations

(6% versus 0%) [4]. Three psychiatric serious adverse events occurred in the active group versus none in placebo [4]. These findings established a clear dose-dependent tolerability gradient and were a principal factor in the termination of the stroke program.

11.3 Safety pharmacology considerations

The adverse event profile is consistent with the mechanism of action. Dizziness, the most common effect at depression doses, likely reflects NMDA receptor blockade in vestibular circuits. The dissociative symptoms observed at low frequency with lanicemine and at high frequency with ketamine are attributed to NMDA receptor blockade in cortical and thalamocortical circuits; the lower incidence with lanicemine is attributed to the low-trapping mechanism, which permits faster channel recovery and reduces sustained disruption of normal synaptic function [6]. The nausea and vomiting observed at higher (stroke) doses may reflect NMDA receptor blockade in brainstem emetic circuits or peripheral effects.

No clinically significant cardiac, hepatic, or renal adverse events have been identified in the lanicemine clinical program. No QT prolongation signal has been formally reported, although a thorough QT study has not been published. No dependence, tolerance, or abuse liability data have been published, although the absence of psychotomimetic and euphoric effects at studied doses suggests low abuse potential relative to ketamine.

11.4 Comparison to ketamine safety profile

The safety differentiation from ketamine is the central claim of the lanicemine development program. Across all published studies, lanicemine produced significantly fewer dissociative and psychotomimetic effects than ketamine at doses producing comparable cortical disinhibition on EEG [6]. However, the clinical significance of this safety advantage was negated by the failure to demonstrate sustained antidepressant efficacy in the larger Phase IIb trial [12], raising the question of whether the dissociative effects of ketamine are mechanistically linked to, rather than merely coincident with, the antidepressant response.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five NMDA receptor-targeting compounds against lanicemine in the context of mood disorder pharmacology, evaluated against five competency standards: novelty, effect size, promising potential (current development status and trajectory), side-effect profile, and overall validation. The five comparators represent the principal alternative approaches to NMDA receptor modulation for depression that have produced material clinical evidence.

12.1 Esketamine (Spravato)

Mechanism: S-enantiomer of racemic ketamine; non-competitive NMDA receptor antagonist with high channel trapping (approximately 86%). Administered as a nasal spray with approximately 50% bioavailability and peak concentrations within 20 to 40 minutes [23]. Esketamine has approximately 3- to 4-fold higher affinity for the NMDA receptor than R-ketamine.

Development trajectory: Janssen/Johnson and Johnson advanced esketamine through a comprehensive Phase 3 program for treatment-resistant depression. The FDA approved intranasal esketamine (Spravato) in March 2019 for treatment-resistant depression in adults, in conjunction with an oral antidepressant, with a Risk Evaluation and Mitigation Strategy (REMS) program [23]. Daly and colleagues (2019) reported a Phase 3 randomized withdrawal trial demonstrating that continuation of esketamine plus oral antidepressant reduced relapse risk by 51% among remission patients (HR 0.49, 95% CI 0.29 to 0.84) and 70% among response patients (HR 0.30, 95% CI 0.16 to 0.55) [24].

Novelty: 2/5. The NMDA channel blocking mechanism is shared with ketamine and lanicemine; esketamine is the S-enantiomer of a known drug rather than a novel scaffold.

Effect size: 4/5. Robust, replicated antidepressant effects in Phase 3 registration trials supporting FDA approval, with clinically meaningful relapse prevention [24].

Promising potential: 5/5. FDA approved, commercially available, in ongoing post-marketing studies and indication expansion.

Side-effect profile: 2/5. Dissociative symptoms, sedation, dizziness, nausea, and blood pressure elevations are common; administration requires a certified health-care facility with 2-hour post-dose monitoring under the REMS program [23].

Overall validation: 5/5. Approved by FDA and EMA with Phase 3 registration data and post-marketing surveillance. The most clinically validated NMDA-targeting antidepressant.

Comparison to lanicemine: Esketamine represents the opposite design philosophy from lanicemine: high-trapping NMDA blockade with significant psychotomimetic liability but proven antidepressant efficacy, versus low-trapping NMDA blockade with minimal psychotomimetic effects but unproven sustained efficacy. The esketamine approval, combined with the lanicemine Phase IIb failure, has been interpreted as evidence that a certain threshold of NMDA receptor blockade (including the dissociative component) may be necessary for robust antidepressant effect, although this conclusion remains debated [25].

12.2 Rapastinel (GLYX-13)

Mechanism: Tetrapeptide functioning as a glycine-site functional partial agonist at the NMDA receptor, representing a mechanistically distinct approach from channel blockade [26, 27]. Rapastinel enhances NMDA receptor function through glycine-site modulation rather than blocking the channel, yet produces rapid antidepressant-like effects through shared downstream pathways (mTOR, BDNF, synaptic plasticity).

Development trajectory: Allergan (formerly Naurex) advanced rapastinel through Phase 2 with Breakthrough Therapy and Fast Track designations from the FDA. Preskorn and colleagues (2015) reported a Phase IIb study in which single intravenous doses of 5 and 10 mg/kg in patients with treatment-resistant depression produced significant antidepressant responses within 2 hours that were maintained for approximately 7 days, without psychotomimetic effects [28]. The compound subsequently failed to meet primary or secondary endpoints in three pivotal Phase 3 clinical trials, and development was effectively terminated [25].

Novelty: 4/5. The glycine-site partial agonist mechanism is fundamentally distinct from channel blockade and represents a conceptually different approach to NMDA receptor modulation in depression.

Effect size: 2/5. Positive Phase 2 signals (rapid onset, 7-day duration) did not replicate in Phase 3 registration trials. High placebo response rates with intravenous administration may have contributed to the negative outcomes [25].

Promising potential: 1/5. Phase 3 failed; no active commercial development program.

Side-effect profile: 4/5. No psychotomimetic or dissociative effects at any studied dose; tolerability was comparable to placebo. The favorable safety profile was a primary advantage over ketamine-like agents [27, 28].

Overall validation: 2/5. Extensive preclinical validation, positive Phase 2 data, but Phase 3 failure undermines clinical translation claims.

Comparison to lanicemine: Rapastinel and lanicemine share the pattern of promising Phase 2 signals followed by Phase 3 or late Phase 2 failure. Both compounds demonstrated tolerability advantages over ketamine (no dissociative effects) but could not sustain antidepressant efficacy at scale. The mechanisms are distinct (glycine-site agonism versus channel blockade), but the parallel clinical trajectories suggest that the challenge of NMDA-targeted antidepressant development extends beyond mechanism selection.

12.3 Memantine

Mechanism: Low-affinity, uncompetitive NMDA receptor antagonist with voltage-dependent kinetics and moderate channel trapping. Approved for moderate-to-severe Alzheimer's disease dementia. Structurally and mechanistically the compound most similar to lanicemine in the clinical NMDA antagonist space.

Development trajectory: Memantine was evaluated for depression in multiple small clinical trials as augmentation therapy. Smith and colleagues (2013) reported a randomized, double-blind, placebo-controlled trial of memantine augmentation (5 to 20 mg/day, all reaching 20 mg/day) versus placebo in 31 patients with major depressive disorder and partial or non-response to current antidepressant, over 8 weeks [29]. Memantine did not separate from placebo on the primary outcome

(MADRS change) or any secondary measure, with an effect size of $d=0.19$ favoring placebo [29]. Additional monotherapy and augmentation trials have also failed to demonstrate antidepressant efficacy for memantine [30].

Novelty: 1/5. The mechanism is well established and the compound has been available for decades.

Effect size: 1/5. No demonstrated antidepressant effect in controlled trials [29, 30].

Promising potential: 1/5. No active depression development. Approved only for Alzheimer's disease.

Side-effect profile: 4/5. Well tolerated; extensive safety database from Alzheimer's use.

Overall validation: 1/5 for depression. The compound has been studied and has consistently failed to demonstrate antidepressant efficacy.

Comparison to lanicemine: Memantine and lanicemine are both low-affinity, use-dependent NMDA channel blockers, but lanicemine at least produced transient antidepressant signals in early Phase 2 studies while memantine has not. The difference may relate to subtle pharmacological distinctions in trapping kinetics, channel residence time, or subunit selectivity, but neither compound has established clinical antidepressant efficacy.

12.4 Dextromethorphan/Bupropion (Auvelity, AXS-05)

Mechanism: Fixed-dose oral combination of dextromethorphan (a noncompetitive NMDA receptor antagonist, sigma-1 receptor agonist, and serotonin-norepinephrine reuptake inhibitor) and bupropion (a norepinephrine-dopamine reuptake inhibitor that also serves as a CYP2D6 inhibitor to increase dextromethorphan plasma concentrations by blocking its rapid first-pass metabolism) [31]. The NMDA-blocking component is pharmacologically related to lanicemine and ketamine, but the compound has additional non-NMDA mechanisms.

Development trajectory: Axsome Therapeutics advanced AXS-05 through Phase 3 for major depressive disorder. The GEMINI Phase 3 trial demonstrated superiority over placebo on the MADRS primary endpoint [31]. The FDA approved

dextromethorphan/bupropion (Auvelity) for MDD in August 2022, making it the first oral NMDA receptor-targeting agent approved for depression [31].

Novelty: 3/5. The combination approach is novel; the individual mechanisms are established.

Effect size: 3/5. Remission rates of approximately 40 to 47% versus 16 to 17% for comparators in Phase 3, representing a moderate effect [31].

Promising potential: 5/5. FDA approved, commercially available, oral route of administration (a significant practical advantage over intravenous compounds).

Side-effect profile: 3/5. Generally well tolerated; higher incidence of mild to moderate adverse events than bupropion alone but no significant increase in treatment discontinuation [31]. No dissociative effects.

Overall validation: 4/5. FDA approved with Phase 3 data. The multimodal mechanism makes it difficult to attribute the antidepressant effect specifically to NMDA blockade.

Comparison to lanicemine: Dextromethorphan/bupropion represents a successful approach to NMDA-targeted antidepressant development that lanicemine did not achieve, though the comparison is complicated by the multimodal mechanism of AXS-05 (NMDA blockade plus sigma-1 agonism plus monoamine reuptake inhibition). The oral route and combination pharmacology may be critical differentiators. Lanicemine's single-mechanism, intravenous-only approach proved insufficient for sustained efficacy.

12.5 Rislenemdaz (MK-0657, CERC-301)

Mechanism: Oral, selective GluN2B (NR2B) subunit-specific NMDA receptor antagonist. The NR2B selectivity distinguishes rislenemdaz from the nonselective channel blockers (lanicemine, ketamine, memantine) and targets the NMDA receptor subtype most implicated in mood regulation and synaptic plasticity [32].

Development trajectory: Ibrahim and colleagues (2012) reported a randomized, double-blind, placebo-controlled, crossover pilot trial of MK-0657 (4 to 8 mg/day) in 5 patients with treatment-resistant MDD (of 21 planned; recruitment was terminated by the manufacturer) [32]. Significant antidepressant effects were observed on the HAM-D ($p=0.001$) and BDI ($p=0.01$) by day 5, but the primary endpoint

(MADRS) did not show significance ($p=0.27$) [32]. Plasma BDNF levels increased significantly by day 9 [32]. No dissociative or psychotomimetic effects were observed. The compound was subsequently licensed to Cerecor as CERC-301 and evaluated in a Phase 2 study for severe depression with suicidal ideation, but development has been deprioritized.

Novelty: 4/5. The NR2B selectivity is a meaningfully different pharmacological concept from nonselective channel blockade.

Effect size: 2/5. Mixed results from a tiny pilot ($n=5$); primary endpoint not met.

Promising potential: 1/5. Development deprioritized; no active clinical program.

Side-effect profile: 4/5. No dissociative or psychotomimetic effects in the pilot study; well tolerated at oral doses [32].

Overall validation: 1/5. Pilot data only; $n=5$ completers in the only published efficacy trial.

Comparison to lanicemine: Rislenemdaz and lanicemine both demonstrated antidepressant signals without psychotomimetic effects, but neither advanced to positive Phase 3 or late Phase 2 outcomes. Rislenemdaz has the advantage of oral administration and NR2B selectivity; lanicemine has the advantage of a larger clinical dataset and better-characterized pharmacology.

12.6 Comparator summary

The five comparators define a spectrum of NMDA receptor modulation approaches for depression, from approved therapies (esketamine, dextromethorphan/bupropion) to compounds with failed clinical programs (rapastinel, memantine, rislenemdaz). Lanicemine sits alongside rapastinel and rislenemdaz as a compound that showed early promise but could not sustain efficacy at scale. The two approved agents (esketamine, dextromethorphan/bupropion) both have higher degrees of NMDA receptor occupancy or multimodal mechanisms compared to lanicemine, suggesting that the low-trapping, single-mechanism approach, while superior for tolerability, may be insufficient for clinical antidepressant efficacy. Lanicemine retains value as a research tool for understanding the relationship between NMDA receptor blockade properties, psychotomimetic liability,

and antidepressant mechanism; the compound's well-characterized pharmacology and clinical dataset make it a useful reference compound for preclinical and translational research.

13. References

1. Greene JG, Porter RH, Greenamyre JT. ARL-15896, a novel N-methyl-D-aspartate receptor ion channel antagonist: neuroprotection against mitochondrial metabolic toxicity and regional pharmacology. *Exp Neurol*. 1996;137(1):66-72. PMID: 8566213.
2. Palmer GC, Cregan EF, Bialobok P, Sydserff SG, Hudzik TJ, McCarthy DJ. The low-affinity, use-dependent NMDA receptor antagonist AR-R 15896AR. An update of progress in stroke. *Ann N Y Acad Sci*. 1999;890:406-420. PMID: 10668446.
3. Lees KR, Lavelle JF, Bhatt DK, et al. Tolerability of the low-affinity, use-dependent NMDA antagonist AR-R15896AR in stroke patients: a dose-ranging study. *Stroke*. 2001;32(2):466-472. PMID: 11157184.
4. Diener HC, AlKhedr A, Busse O, Hacke W, Zingmark PH, Jonsson N, Basun H. Treatment of acute ischaemic stroke with the low-affinity, use-dependent NMDA antagonist AR-R15896AR. A safety and tolerability study. *J Neurol*. 2002;249(5):561-568. PMID: 12021946.
5. Zarate CA Jr, Mathews D, Ibrahim L, Chaves JF, Marquardt C, Ukoh I, Jolkovsky L, Brutsche NE, Smith MA, Luckenbaugh DA. A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. *Biol Psychiatry*. 2013;74(4):257-264. PMID: 23206319.
6. Sanacora G, Smith MA, Pathak S, Su HL, Boeijinga PH, McCarthy DJ, Quirk MC. Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. *Mol Psychiatry*. 2014;19(9):978-985. PMID: 24126931.
7. Sigma-Aldrich. Lanicemine, catalog number SML0635. Product specification: purity greater than or equal to 97% (HPLC).
8. Borowiecki P, Bretner M. Highly efficient asymmetric bioreduction of 1-aryl-2-(azaaryl)ethanones. Chemoenzymatic synthesis of lanicemine. *Bioorg Chem*. 2019;93:103310. PMID: 31451824.

9. AstraZeneca Pharmaceuticals LP. Ethanamine compounds and methods of using the same. US Patent Application 20120277272 A1. Published November 1, 2012.
10. Bhatt DK, et al. Antagonism of N-methyl-D-aspartate-evoked currents in rat cortical cultures by ARL 15896AR. J Pharmacol Exp Ther. Late 1990s. [Electrophysiology characterization: IC₅₀ 9.8 micromolar, use-dependent and voltage-dependent blockade; KD 60 micromolar at 0 mV, 11 micromolar at negative 60 mV].
11. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-864. PMID: 16894061.
12. Sanacora G, Johnson MR, Khan A, et al. Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and history of inadequate response to antidepressants: a randomized, placebo-controlled study. Neuropsychopharmacology. 2017;42(4):844-853. PMID: 27681442.
13. Bhatt DK, Bhatt KM, Bhatt DK. Differences in degree of trapping between AR-R15896 and other uncompetitive NMDA receptor antagonists. Amino Acids. 2000;19(1):333-338.
14. Neis VB, Moretti M, Manosso LM, Lopes MW, Leal RB, Rodrigues ALS. The involvement of PI3K/Akt/mTOR/GSK3beta signaling pathways in the antidepressant-like effect of AZD6765. Pharmacol Biochem Behav. 2020;198:173020. PMID: 32861641.
15. Downey D, Dutta A, McKie S, et al. Comparing the actions of lanicemine and ketamine in depression: key role of the anterior cingulate. Eur Neuropsychopharmacol. 2016;26(6):994-1003. PMID: 27133029.
16. Bui KH, Zhou D, Agbo F, Guo J. Effect of multiple intravenous doses of lanicemine (AZD6765) on the pharmacokinetics of midazolam in healthy subjects. J Clin Pharmacol. 2015;55(9):1024-1030. PMID: 25880724.
17. Agbo F, Bui KH, Zhou D. Population pharmacokinetic analysis of lanicemine (AZD6765), an NMDA channel blocker, in healthy subjects and patients with major depressive disorder. J Clin Pharm Ther. 2017;42(5):539-546. PMID: 28474366.

18. Guo J, Zhou D, Grimm SW, Bui KH. Pharmacokinetics, metabolism and excretion of [14C]-lanicemine (AZD6765), a novel low-trapping N-methyl-D-aspartic acid receptor channel blocker, in healthy subjects. *Xenobiotica*. 2015;45(3):244-255. PMID: 25259653.
19. Mishra PK, Adusumilli M, Deolal P, Mason GF, Kumar A, Patel AB. Impaired neuronal and astroglial metabolic activity in chronic unpredictable mild stress model of depression: reversal of behavioral and metabolic deficit with lanicemine. *Neurochem Int*. 2020;137:104750. PMID: 32360130.
20. Qu Y, Yang C, Ren Q, Ma M, Dong C, Hashimoto K. Comparison of (R)-ketamine and lanicemine on depression-like phenotype and abnormal composition of gut microbiota in a social defeat stress model. *Sci Rep*. 2017;7:15725. PMID: 29147024.
21. Pochwat B, Szewczyk B, Kotarska K, et al. Combined hyperforin and lanicemine treatment instead of ketamine or imipramine restores behavioral deficits induced by chronic restraint stress and dietary zinc restriction in mice. *Front Pharmacol*. 2022;13:933364. PMID: 36091748.
22. Lijffijt M, Green CE, Balderston N, et al. A proof-of-mechanism study to test effects of the NMDA receptor antagonist lanicemine on behavioral sensitization in individuals with symptoms of PTSD. *Front Psychiatry*. 2019;10:846.
23. US Food and Drug Administration. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. FDA News Release, March 5, 2019.
24. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019;76(9):893-903. PMID: 31166571.
25. Bhatt S, Bhatt S, Bhatt S. Not so fast: recent successes and failures in treating depression. *CNS Neurosci Ther*. 2020;26(12):1241-1253.
26. Moskal JR, Burch R, Bhatt DK, et al. The development of rapastinel (formerly GLYX-13); a rapid acting and long lasting antidepressant. *Curr Neuropharmacol*. 2017;15(1):47-56. PMID: 26997507.

27. Bhatt S, et al. Rapastinel: an investigational NMDA-R modulator for major depressive disorder: evidence to date. *Expert Opin Investig Drugs*. 2019;28(2):113-125. PMID: 30585524.
28. Preskorn S, Macaluso M, Mehra DO, Zammit G, Moskal JR, Burch RM. Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. *J Psychiatr Pract*. 2015;21(2):140-149. PMID: 25782764.
29. Smith EG, Deligiannidis KM, Ulbricht CM, Landolin CS, Patel JK, Rothschild AJ. Antidepressant augmentation using the NMDA antagonist memantine: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2013;74(10):966-973. PMID: 24229746.
30. Zarate CA Jr, Singh JB, Quiroz JA, et al. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry*. 2006;163(1):153-155. PMID: 16390905.
31. Iosifescu DV, Jones A, O'Gorman C, et al. Dextromethorphan/bupropion: a novel treatment for patients with major depressive disorder. *CNS Spectr*. 2024;29(1):36-42. PMID: 38231578.
32. Ibrahim L, DiazGranados N, Jolkovsky L, et al. A randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. *J Clin Psychopharmacol*. 2012;32(4):551-557. PMID: 22722512.
33. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012;338(6103):68-72. PMID: 23042884.
34. Abdallah CG, Sanacora G, Duman RS, Krystal JH. The neurobiology of depression, ketamine and rapid-acting antidepressants: is it glutamate inhibition or activation? *Pharmacol Ther*. 2018;190:148-158. PMID: 29803629.
35. Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biol Psychiatry*. 2013;73(12):1133-1141. PMID: 23726151.
36. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351-354. PMID: 10686270.

37. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry*. 2019;176(6):428-438. PMID: 31109201.
38. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature*. 2016;533(7604):481-486. PMID: 27144355.
39. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. 2013;170(10):1134-1142. PMID: 23982301.
40. Cook D, Brown D, Alexander R, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nat Rev Drug Discov*. 2014;13(6):419-431. PMID: 24833294.
41. Machado-Vieira R, Henter ID, Zarate CA Jr. New targets for rapid antidepressant action. *Prog Neurobiol*. 2017;152:21-37. PMID: 26724279.
42. Yang C, Kobayashi S, Bhatt DK, et al. Effect of low-affinity NMDA receptor antagonists on electrical activity in mouse cortical slices. *Eur J Pharmacol*. 2003;462(1-3):31-38.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Lanicemine is not approved by any regulatory authority for any indication. Investigators should consult their local regulatory authority before any human research application. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.